FORMULATION AND EVALUATION OF GLIMEPIRIDE AS GASTRO RETENTIVE DOSAGE FORM

Dissertation work submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

in partial fulfillment of the award of degree of
MASTER OF PHARMACY (PHARMACEUTICS)

March 2009

COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
Coimbatore – 641 044

CERTIFICATE

This is to certify that the dissertation entitled

FORMULATION AND EVALUATION OF GLIMEPIRIDE AS GASTRO RETENTIVE DOSAGE FORM

was carried out by

C. RUBINA REICHEL

in the Department of Pharmaceutics College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to the Tamilnadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and complete satisfaction.

Dr. J.Bagyalakshmi, M.Pharm., Ph.D.,
Assistant Professor,
Department of Pharmaceutics,
College of Pharmacy, SRIPMS, Coimbatore.

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Dr.M.Gopal Rao, M.Pharm., Ph.D.,
Vice Principal,
Head, Department of Pharmaceutics,
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Date:

Dedicated to

Lord & Saviour

Jesus Christ and

My Daddy

ACKNOWLEDGEMENT

"Behind any achievement there are many helping hands that aid in reaching the ultimate goal"

I consider it as a great honour to express my deep sense of gratitude and indebtedness to ***Dr.J.Bagyalakshmi, M.Pharm., Ph.D***., Assistant Professor, Dept. of Pharmaceutics, who not only guided at every step of my research work, but also kept me in high spirits through her valuable suggestions and inspiration.

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I submit my sincere thanks to our beloved ***Managing Trustee Dr.R.Venkatesalu Naidu*** for providing all the facilities to carry out this thesis work.

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I remain great indebted to my beloved ***parents, loving husband, daughter and brother*** for their precious love, affection, prayers and moral support which guided me in the right path and are also the backbone for all successful endeavors in my life.

Above all, I humbly submit my dissertation work into the hands of ***Almighty*** who is the source of all wisdom and knowledge for the successful completion of my thesis.

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INTRODUCTION

GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesive [Ponchel G and Irache JM, 1998; Shweta Arora, et.al. 2005], flotation [Deshpande A, et.al. 1997], sedimentation [Rednick AB and Tucker SJ, 1970; Davis SS, et.al. 1986], expansion [Urguhart J and Theeuwes F, 1994; Mamajek RC and Moyer ES, 1980], modified shape system [Fix JA, et. al. 1993; Kedzierewicz F, et.al. 1999] or by the simultaneous administration of pharmacological agents [Groning R and Heun, 1984; 1989] that delay gastric emptying.

Floating drug delivery system is also referred as Hydrodynamically Balanced System (HBS) or Gastro Retentive Drug Delivery System (GRDDS).

FACTORS AFFECTING GASTRIC RETENTION

Gastric residence time of an oral dosage form is affected by several factors.

1. Gastric pH

The pH of the stomach in fasting state is 1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents 6.0 to 9.0.

2. Formulation factor

2.1 Pattern or nature of the dosage form

Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multi-particulate formulations as compared with single unit formulation. [Bechgaard H and Ladefoged K, 1978]

2.2 Size and shape of dosage form

Size and shape of dosage form also affect the gastric emptying. Garg and Sharma [Garg S and Sharma S, 2003] reported that tetrahedron and ring-shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

2.3 Density of the dosage form

The density of the dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats.

Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. [Shweta Arora, et.al. 2005]

3. Food intake

A comparison was made to study the affect of fed and non fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach. [Shweta Arora, et.al. 2005]

4. Fluid volume

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. [Shweta Arora, et.al. 2005]

5. Biological factors

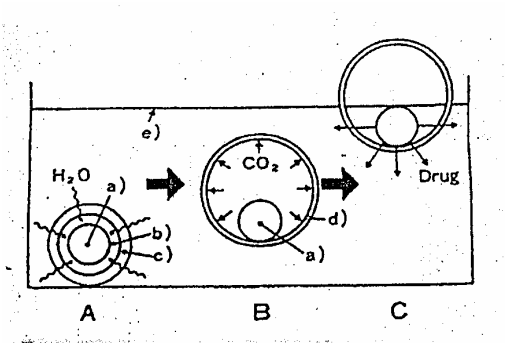
Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. [Singh BN and Kim KH, 2000]

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

Floating Drug Delivery Systems are classified depending on the use of two formulation variables. They are Effervescent and Non-effervescent systems.

EFFERVESCENT FLOATING DOSAGE FORM

These are matrix type of system prepared with the help of swellable polymers such as Methyl cellulose and various effervescent compounds e.g. Sodium carbonate, Tartaric acidic and Citric acid. They are formulated in such a way that when in contact with the acidity gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form. [Shweta Arora, et.al. 2005]



A) Penetration of water

B) Generation of CO_2 & floating

C) Dissolution of drug

Figure 1: Stages of floating mechanism

NON-EFFERVESCENT FLOATING DOSAGE FORM

Non-effervescent floating dosage form use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation

method includes a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of <1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. [Shweta Arora, et.al. 2005]

Sheth and Tossounian [Sheth PR and Tossounian JL, 1978] developed an Hydrodynamically Balanced System containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released (Figure 2).

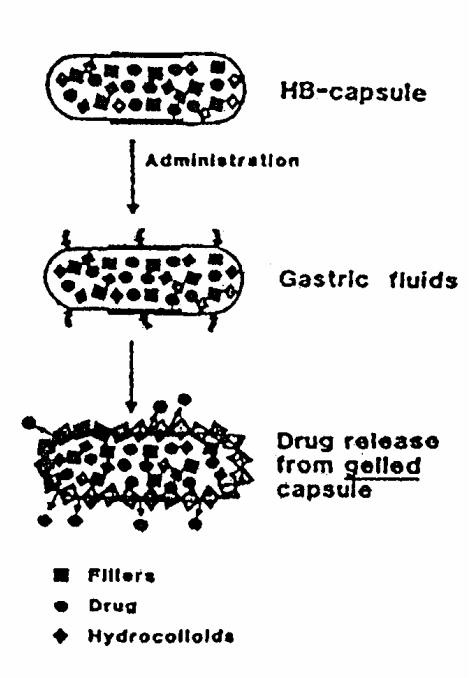


Figure 2: Working principle of the hydrodynamically balanced system

Sheth and Tossounian [Sheth PR and Tossounian JL, 1979] developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic

hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids. (Figure 3 A and B)

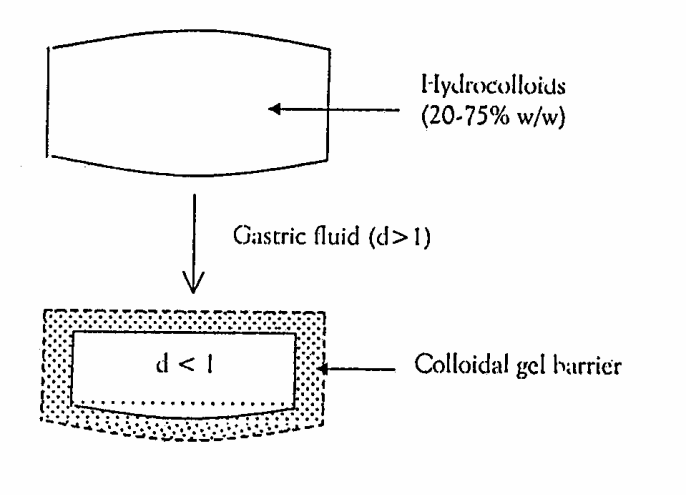


Figure 3: (A) Intra gastric floating tablet

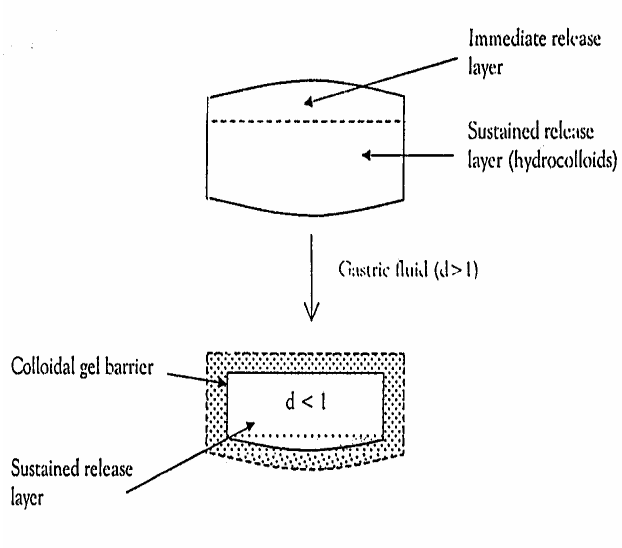


Figure 3: (B) Intra gastric floating bilayer tablet

FLOATING DRUG DELIVERY SYSTEM MECHANISM

As per mechanism of expansion of expandable dosage form, the generation of gas on contact with gastric juice is preferred. While various gases will be suitable from the physiological point of view, among of them, nitrogen, nitrous oxide, methane and other gases, expansion with CO_2 is particularly preferred since this can be released readily and in a relatively large amount. In principle suitable substance from which CO_2 can be released are various carbonates and hydrogen carbonates. On account of good tolerability and high yield, Hydrogen Carbonate ($NaHCO_3$) or Sodium Hydrogen Carbonate is preferred. [Asmussen B, et.al. 2001]

APPROACHES TO DESIGN FLOATING DOSAGE FORMS

The following approaches have been used for the design the floating dosage form of single unit system.

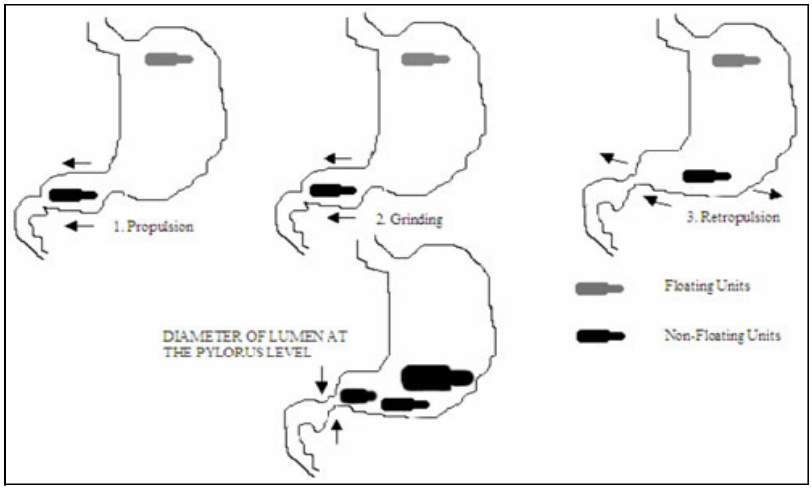


Figure 4: Intra gastric residence positions of floating and non-floating units

Single-Unit Dosage Forms

In Low-density approach [Deshpande AA, et.al. 1997] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells24 popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

Fluid- filled floating chamber [Joseph NJ, et.al. 2002] type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the

gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/ml and is ~0.1 mg/ml at neutral pH).

HBS of chlordiazeopoxide hydrochloride had comparable blood level time profile as of three 10-mg commercial capsules. HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropylmethylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a disproportionate 3-layer matrix technology to control drug release.

The 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and

achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process. The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

1) Sustained Drug Delivery

HBS can remain in the stomach for longer period and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with a CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Similarly a comparative study [Erni W and Held K, 1987] between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours. *In vitro* in the former case and the release was essentially complete in less than 30 minutes in the latter case.

2) Site specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine e.g. Riboflavin and Furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that in monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those conventional Furosemide tablets. [Menon A, et.al. 1994]

3) Absorption enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. Miyazaki S, et.al. [Miyazaki S, et.al. 1988] conducted pharmacokinetic studies on floating granules of Indomethacin prepared with chitosan and compared the peak plasma concentration and AUC with the conventional commercially available capsules. It was concluded that the floating granules prepared with chitosan were superior in terms of decrease in peak plasma concentration and maintenance of drug in plasma. Ichikawa M, et.al. [Ichikawa M, et.al. 1991] developed a multiparticulate system that consisted of floating pills of a drug (P– amino benzoic acid) having a limited absorption site in the gastrointestinal tract. It was forced to have 1.61 times greater AUC than the control pills.

LIMITATION OF FLOATING DRUG DELIVERY SYSTEM

Floating Drug Delivery System (FDDS) is associated with certain limitations. Drugs that irritate the mucous, those that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms.

Flotation as a retention mechanism requires the presence of liquid on which the dosage form can float on the gastric contents [Chitnis V, et.al. 1991], or the dosage form can be administered with a full glass of water to provide the initial fluid for buoyancy. Also single unit floating capsules or tablets are associated with an “all or none concept”, but this can be overcome by formulating multiple units system like floating microspheres (or) micro balloons. [Rouge N, et.al. 1997]

BACKGROUND OF THE INVESTIGATION

Diabetes Mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. [Diabetes care 2004] Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs especially the eyes, kidney, nerves, heart, and blood vessels.

Classification of Diabetes Mellitus

Type 1 : Diabetes Mellitus: (β-cell destruction usually leading to absolute insulin deficiency)

Type 2 : Diabetes Mellitus.

Importance of oral medication in diabetes

Oral medication for the management of Type 2 diabetes has been available in the US since 1957, when the sulfonyl urea drug Tolbutamide was approved by the FDA. This was followed in the year 1950's and 1960's by the approval of other first generation sulfonyl urea – Chlorpropamide, Acetohexamide, and Tolazolamide.

Second generation sulfonyl urea – Glipizide and Glyburide were introduced in the year 1984. More than a decade later in 1995, the biguanide, Metformin was approved by the FDA, followed in 1996 by Glimepiride a sulfonyl urea, drug – Agarbose α-glucosidase inhibitor.

In 1997 – Trogilitazone the first Thiazolidinedione – insulin sensitizer was approved, but it was withdrawn in 2000 due to liver toxicity. Thiazolidinedione

insulin sensitizer, Rosiglitazone, and Pioglitzone, the second glucosidase inhibitor Migilitol were marketed beginning in 1999.

Table 1: Dispensed outpatient prescription for oral antidiabetic medication in US [Diane K.W, et.al. 2003]

Generic Name	Trade Name	Year of approved
Sulfonyl Ureas		
Tolbutamide	Orinase	1957
Chlorpropamide	Diabinese, Glucamide	1958
Acetohexamide	Dymelor	1964
Tolazomide	Tolinase	1966
Glipizide	Glucotrol, Glucotrol XL	1987
Glyburide	Diabeta, Micronase, Glynase	1984
GLIMEPIRIDE	**Amaryl**	**1996**
Biguanide		
Metformin	Glucophage	1995
Glycosidase inhibitors		
Agarbose	Precose	1995
Migilitol	Glyset	1999
Thiazolidinedione insulin sensitizer		
Troglitazone	Rezulin	1997
Rosiglitazone	Avandia	1999
Pioglitazone	Actos	1999
Non Sulfonyl Urea Insulin Secretagogues		
Repaglinide	Prandin	1998
Nateglinide	Starlix	2001

In 1999 23.4 million, outpatient prescription for oral antidiabetic medication were dispensed in US. By 2001 this number had increased 3.9 fold to 94.84 million prescriptions.

Through 1996, the market was dominated by use of second generation sulphonyl urea medication, Glyburide, Glipizide, and Glimepiride. These medications together accounted for 77% of prescription in 1990 and 75% of prescription in 1996. No sustained release dosage form for Glimepiride is available till date.

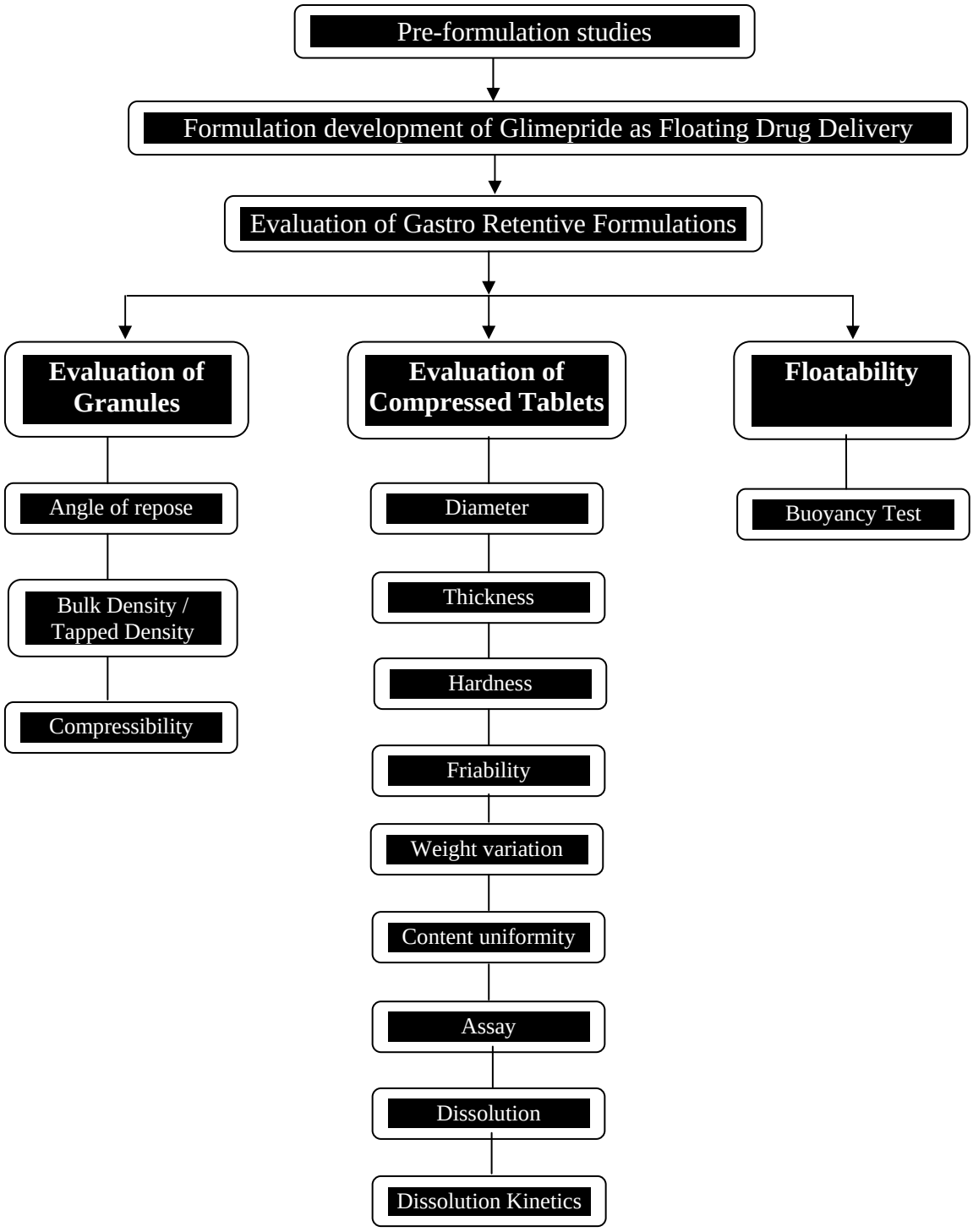
OBJECTIVES

Gastro Retentive Drug Delivery Systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. It has been reported that in monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. Hydrodynamically Balanced System (HBS) can remain in the stomach for longer periods and hence can release the drug over a prolonged period of time encountered with a Controlled Release formulation hence can be overcome with these systems. [Shweta Arora, et.al. 2005]

The bioavailability of certain antidiabetic drugs reduces due to the pathophysiology of the patient. In such cases prolonged gastric retention of the therapeutic moiety may offer numerous advantages, including improved bioavailability, therapeutic efficiency and possible reduction of dose.

Glimepiride is second generation new sulfonyl urea oral antidiabetic. Glimepiride is poorly soluble in acidic environment. When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients due to impaired gastric motility or gastric emptying. This erratic absorption of Glimepiride becomes clinically significant, since the efficacy of short acting sulfonylurea is dependent upon the absorption rate of the drug. Hence, to overcome the above mentioned drawbacks the present study aims to develop Glimepiride as Floating Drug Delivery System (FDDS) and its evaluation.

PLAN OF WORK


Pre-formulation studies
Formulation development of Glimepride as Floating Drug Delivery
Evaluation of Gastro Retentive Formulations
Evaluation of Granules
Angle of repose
Bulk Density / Tapped Density
Compressibility
Evaluation of Compressed Tablets
Diameter
Thickness
Hardness
Friability
Weight variation
Content uniformity
Assay
Dissolution
Dissolution Kinetics
Floatability
Buoyancy Test

LITERATURE REVIEW

Abubakr O. Nur and Jun S. Zhang (2000), [Abubakr O. Nur, et.al. 2000] Two viscosity grades of Hydroxypropylmethylcellulose (HPMC 4000 and 15000 cps) and Carbopol 934P were used to prepare Captopril floating tablets. *In vitro* dissolution was carried out in simulated gastric fluid (enzyme free) at 37 ± 0.1ºC using the USP apparatus 2 basket method. Compared to conventional tablets release of Captopril from these floating tablets was apparently prolonged; as a result, a 24-hr controlled-release dosage form for Captopril was achieved. Drug release best fit both the Higuchi model and the Korsmeyer and Peppas equation, followed by first order kinetics. While tablet hardness and stirring rate had no or little effect on the release kinetics, tablets hardness was found to be a determining factor with regard to the buoyancy of the tablets.

Anand Kumar, Sri Vastava, Devendra Narayanrao Ridhurkar, Saurabh Wadhwa (2005), [Anand Kumar, et.al. 2005], Involves preparation and evaluation of floating microspheres with Cimetidine as model drug for prolongation of gastric residence time. *In vitro* studies demonstrated diffusion controlled drug release from the microspheres.

Arati A. Dehpande, Navnit H. Shah: Christopher T. Rhodes, and Waseem Malick (1997), [Arati A. Dehpande, et.al. 1997], report on the development of a novel controlled- release gastric retention system, which consists of a matrix tablet, coated with a permeable membrane. When immersed in simulated gastric fluid,

the tablet expands. The tablet remains expanded for eighteen to twenty hours, during which time the drug is released. The tablet then either disintegrates into fragments or loses its integrity.

Asha Patel, Subhabrata Ray, Ram Sharnagat Thakur (2006), [Asha Patel, et.al. 2006], the floating microshperes have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formulation. The major advantage of the preparation technique includes short processing time, the lack of exposure of the ingredients to high temperature and high encapsulation efficiencies. In the present study, preparation of Metformin hydrochloride floating microspheres, evaluation of Drug Dosage System *in vitro*, prediction of the release and optimization of floatation of drug release pattern to match target release profile was investigated. The developed floating microspheres of Metformin hydrochloride may be used in clinic for prolonged drug release in stomach for at least 8 hours. There by improving the bioavailability and patient compliance.

Baumgartner S, et.al. [Baumgartner S, et.al. 2000], developed a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant. *In vivo* experiments with fasted state beagle dogs revealed prolonged gastric residence time. The comparison of gastric motility and stomach emptying between humans and dogs showed no big difference and therefore it was speculated that the experimentally proven increased

gastric residence time in beagle dogs would be compared with known literature for humans, where this time is less than 2 hours.

Brijesh S. Dave, Avani F, Amin and Madhabhai M. Patel (2004), [Brijesh S. Dave, et.al. 2004], this research was to prepare a Gastric Retentive Drug Delivery System of Ranitidine hydrochloride. These studies indicate that the proper balance between a release rate enhances and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile.

Shweta Arora, Javel Ali, Alka Ahuja, Roop K. Khar, and Sanjula Baboota (2005), [Shweta Arora, et.al. 2005] Floating Drug Delivery System (FDDS) was to compile the recent mechanism of floatation to achieve gastric retention. This review also summarizes the *in vitro* techniques, *in vivo* studies to evaluate the performance and application of floating systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

Hiroshi Yuasa, Yuki Takashima and Yoshio Kanaya (1996), [Hiroshi Yuasa, et.al. 1996], prepared an intragastric floating preparation using porous calcium silicate as a floating carrier, which has floating ability due to the air included in the pores when they are covered with polymer, it also has a sustained drug release property.

Shoufeng Li, Senshang Lin, Bruce P. Daggy, Haresh L. Mirchandani and Yie W.Chien (2002), [Shoufeng Li, et.al. 2002], to evaluate the contributing of formulation variables on the floating properties of a Gastric Floating Drug Delivery System using a continuous floating monitoring system and statistical experiment

design. The effect of formulation variables on the floating property of the delivery system, the effect of formulation variables in the floating property of the delivery system and their ranges could be identified. Incorporation of hydrophobic agents such as Magnesium stearate could significantly improve the floating capacity of the Gastric Floating Drug Delivery System.

Nurten Ozedemir, Sefika Ordu, Yalcin ozkan (2000), [Nurten Ozdemir, et.al. 2000], the purpose of enhancement of the bioavailability of Furosemide, a floating dosage form with controlled release of Furosemide was designed in the study. A floating dosage form with controlled release of Furosemide was designed in this study, a considerably significant correlation was detected between *in vivo* results and *in vitro* data of the dissolution rate, and it was concluded that the modified continuous flow through cell method is usable for *in vitro* dissolution rate test of floating dosage forms.

Libo Yang and Reza Fassihi (1996), [Libo Yang, et.al. 1996], a new approach based on the three layer matrix technology to control drug release for oral administration is presented. Polyethylene oxide polymers of various molecular weights together with Theophylline as drug model and other excipients have been directly compressed into a three-layer asymmetric floatable system. The core layer contains the active drug while external layers with different thickness, composition, and erosion rates are designed to delay the hydration of the middle layer, restrict the early drug diffusion only through cylindrical side surfaces of the tablet, and provide controlled drug release. Results show that during 16hr dissolution study drug is

completely released following the zero-order kinetics with no burst effect. The release rate remains around 0.1mg min^{-1} throughout the dissolution study. The release kinetics is independent of changes in pH and compression force but dependent on layer thickness and formulation components. It appears that the operating release mechanism is based on the existence of a balance between the velocities of advancing glassy/rubbery front and erosion at the swollen polymer / dissolution front.

Hamid A, Merchant, Harris M.Shoaib, Jaweria Tazeen, and Rabia I.Yousuf (2006), [Hamid A. et.al. 2006], Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug release profile, they are cost effective, and they have broad US Food and Drug Administration acceptance. The hydrophilic polymer matrix system consists of hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration, and dissolution for controlled release of drug. At the same time, other soluble excipients or drug substances will also wet, dissolve, and diffuse out of the matrix, where as insoluble excipients or drug substances will be held in place until the surrounding polymer, excipients, or drug complex erodes or dissolves away. Hydroxypropylmethylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is mixed alkyl hydroxyalkylcellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility

of HPMC is pH independent. HPMC has been found to be a very versatile material for the formulation of soluble matrix tablets. It is a widely accepted pharmaceutical excipient and is included in all major compendia. Because HPMC is available in a wide range of molecular weights, effective control of gel viscosity is easily provided.

K. Raghuram Reddy, Srinivas Mutalik, and Srinivas Reddy (2003), [K. Raghuram Reddy, et.al. 2003], the objective of the present study was to develop once-daily sustained release matrix tablets of Nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidine were used as granulating agents along with hydrophilic matrix materials like hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmaco technical properties and complied with in-house specifications for tested parameters. According to the theoretical release profile calculation, a once-daily sustained-release formulation should release 5.92 mg of Nicorandil in 1 hour, like conventional tablets, and 3.21 mg per hour up to 24 hours.

Esra Demirtürk / Levent Öner (2005), [Esra Demirthiirk, et.al. 2005], three categories of dissolution test specifications for immediate release drug products are described in the guidance. Single point specifications are recommended as a routine quality control test for highly soluble and rapidly dissolving drug products. This comparison method can be employed in evaluating scale-up and post-approval changes such as manufacturing site changes, component and composition changes, equipment changes and process changes. Two-point specifications are suggested for characterizing the quality of drug product and for accepting product sameness under SUPAC-related changes. In the presence of certain minor changes the single point dissolution test may be adequate to ensure unchanged product quality and performance. For more major changes a dissolution profile comparison performed under identical conditions for the product before and after the changes is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity and similarity at every dissolution sample time point.

Ozdemir et. al. [Ozdemir et.al. 2000] developed floating layers tablet with controlled release for Furosemide. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times more than that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Choi BY, et. al. [Choi BY, et.al. 2002], prepared floating alginate beads using gas-forming agents (Calcium carbonate and Sodium bicarbonate) and studied the effect of CO_2 generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less effective gas-forming agent than Sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. In-vitro floating studies revealed that the beads free of gas forming agents sank uniformly in the media while the beads containing gas forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

Talwar N, et.al. [Talwar N, et.al. 2001], developed a once daily formulation for oral administration of Ciprofloxacin. The formulation was composed of 69.9% Ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate and 12.1% cross linked poly vinyl pyrrolidine. The viscolysing agent initially and the gel forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine. The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug.

Moursy NM, et.al. [Moursy NM, et.al. 2003], developed sustained release floating capsules of Nicardipine hydrochloride. For floating hydrocolloids of high viscosity grades were used and to aid in buoyancy. Sodium bicarbonate was added to allow evolution of CO_2. In vitro analysis of a commercially available 20mg capsule of Nicardipine hydrochloride (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy.

Nur AO, and Zhang JS [Nur AO and Zhang JS, 2000], developed floating tablets of Captopril using HPMC (4000 and 15000cps) and Carbopol 934P. *In vitro* buoyancy studies revealed that tablets of 2 Kg/cm^2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 Kg/cm^2 sank for 3 to 4 minutes and then came to the surface tablets in both cases remained floating for 24hrs.

Hiroshi Yuasa, Yuki Takashima, and Yoshio Kanaya (1996), [Hiroshi Yuasa, et.al. 1996], prepared an intragastric floating preparation using porous calcium silicate (Florite RE, FLR) as a floating carrier, which has floating ability due to the air included in the pores when they are covered with a polymer, it also has a sustained drug release property. Floating granules were prepared by dropping a 5 or 10% (w/v of ethanol solution of hydroxypropylcellulose (HPC) and ethylcellulose (EC) in 4 different concentration ratios while the Calcium silicate was being agitated in a beaker. After the mixture was dried *in vacuo* and sieved, we regarded the granules obtained as primary coated granules (PCG). After drying, the ethanol solution of the

polymer was dropped and dried *in vacuo* again, and sieving was carried out to obtain secondary coated granules (SCG). The floating property and surface and inner structures of PCG and SCG were studied. Further, we prepared PCG and SCG including Diclofenac sodium (DS) (DS-PCG, DS-SCG) as a model drug, and the release profile from these granules was observed. The floating property of SCG was better than that of PCG. A longer floating time was observed with a higher polymer concentration and a lower HPC composition ratio. It was observed by a scanning electron microscope (SEM) and the pore size distribution that more pores of Calcium silicate in SCG were covered with polymer that those in PCG. DS-SCG showed a smaller release rate than DS-PCG. These suggest that Calcium silicate is a useful floating carrier for the development of floating and sustained release preparations.

Shozo Miyazaki, Hideki Yamaguchi, Chizuko Youkouchi, Masahiko Takada, and Wei-Min Hou (1998), [Shozo Miyazaki, et.al. 1998], the release rate of Indomethacin from chitosan granules was compared with that of conventional commercial Indomethacin capsules and a sustained-release capsule. In contrast with the rapid release of commercial conventional capsule form, sustained release from the chitosan granules was observed. Furthermore, the release rate could be controlled by changing the mixing ratio of drug and chitosan. The potential of chitosan granules as an oral sustained-release dosage form of Indomethacin was investigated in rabbits. When a conventional commercial capsule was administered orally to rabbits, the plasma concentration reached the maximum level 1h after administration. In the case of the granules with a 1:2 mixture of drug and chitosan, the chitosan granules did not

give a sharp peak of plasma concentration, but produced a sustained plateau level of Indomethacin. Area under the plasma concentration curve (AUC) (0-8h) value of chitosan granules showed a slightly higher value than that of commercial capsules. This may be due to slow rate of release from the chitosan granules and the longer residence time in the stomach.

Stanley S. Davis, Anita F. Stockwell, Margaret J. Taylor, John G. Hardy, David R. Whalley, C.G. Wilson, Helle Bechgaard, and Finn N. Christensen (1986), [Stanley S. Davis, et.al. 1986], the gastric emptying of pellets and single units of different densities has been followed in healthy subjects using the technique of gamma scintigraphy. The gastric emptying of the light pellets was affected by their buoyancy in the upper part of the stomach. However, the mean gastric emptying rates of pellets and single units were not significantly affected by density. Floating or buoyant delivery systems may have little advantage over conventional systems. The presence of food in the stomach was found to be the major factor in determining the gastric emptying of single units.

Joseph A. Fix, Robyn Cargill, and Karen Engle (1993), [Joseph A. Fix, et.al. 1993], the performance of controlled-release dosage forms can depend on the location of the dosage form within the gastrointestinal (GI) tract. The ability to retain a dosage form in a specific location of the GI tract, preferably the stomach, would provide constant exposure of the entire absorptive surface of the intestine to the drug being released, thereby optimizing conditions for maximal control of drug absorption.

Subhash Desai and Sanford Bolton (1993), [Subhash Desai, et.al. 1993], A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. The buoyancy was attributed to air and oil entrapped in the agar gel network. A floating controlled release 300mg Theophylline tablet having a density of 0.67 was prepared and compared *in vitro* and *in vivo* to Theodur. The *in vitro* release rate of the floating tablet was slower. *In vivo* scintigraphic studies for a floating and a heavy nonfloating tablet, under fasting and non-fasting conditions, showed that the presence of food significantly increased the gastric retention time for both tablets, and tablet density did not appear to make a difference in the gastric retention time. However, the positions of the floating and non-floating tablets in the stomach were very different. Bioavailability studies in human volunteers under both fasting and non-fasting conditions showed results comparable to those with Theodur. The floating controlled-release Theophylline tablet maintained constant Theophylline levels of about 2mg/mL for 24 hr, which may be attributable to the release from the agar gel matrix and the buoyancy of the tablet in the stomach.

Marianne Oth, Michel Franz, Jacques Timmermans, and Andre Moes, (1992), [Marianne Oth, et.al. 1992], a bilayer floating dosage unit is proposed to achieve local delivery of Misoprostol, a prostaglandin E_1 analogue, at the gastric mucosa level. The system is a capsule consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content and a drug layer formulated to act as a sustained-delivery system. The differential design of the two layers allows the

optimization of both floating capability and drug release profile. The layers are both composed of a hydrophilic matrix based upon hydroxypropylmethyly cellulose (HPMC). Parameters influencing the release profiles are described. The use of a large capsule increases the gastric residence time (GRT), as it impedes passage through the pylorus opening. ϒ-scintigraphic studies were performed to visualize cohesion of the two layers *in vivo* and to determine GRT as a function of meal regimen. The average GRTs were 199 ± 69 min after a single meal (breakfast) and 618 ± 208 min after a succession of meals.

Manoj N. Gambhire, Kshitij W. Ambade, Sushma D. Kurmi, Vilasrao J. Kadam, and Kisan R. Jadhav (2007), [Manoj N. Gambhire, et.al. 2007], the purpose of this research was to prepare a floating drug delivery system of Diltiazem hydrochloride (DTZ). Floating matrix tablets of DTZ were developed to prolong gastric residence time and increase its bioavailability. Rapid gastro- intestinal transit could result incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxypropylmethylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO, alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate and succinic acid on drug release profile and floating properties were investigated. A 3^2 factorial design was applied to systematically optimize the drug release profile. The amounts of Methocel K100M CR (X1) and Compritol 888 ATO (X2) were selected

as independent variables. The time required for 50% (t_{50}) and 85% (t_{85}) drug dissolution were selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR (X1) and Compritol 888 ATO (X2) favors the preparation of floating controlled release of DTZ tablets. Comparable release profiles between the commercial product and the designed system were obtained. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r^2). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Dasharath M. Patel, Natvarlal M. Patel, Nitesh N. Pandya, and Pranav D. Jogani (2007), [Dasharath M. Patel, et.al. 2007], The high cost involved in the development of a new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery systems. Drug release from the delivery devices can be sustained up to 24 hours for many drugs using current release technologies. However, the real issue in the development of oral controlled release dosage forms is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal (GI) tract until the drug is completely released. Rapid GI transit could result incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose. Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, floating systems, and other

delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Carbamazepine (CBZ) is used for anticonvulsant and anti- neuralgic effects. The popularity of this drug is related to several beneficial properties, including proven efficacy in controlling different types of seizures.

DRUG PROFILE

GLIMEPIRIDE, a new generation sulphonyl urea [Michihiro Matsuki, et.al. 2007] has several benefits, rapid and complete absorption after oral administration, a lower dose, long duration action, and possible insulin sensitizing effect. Glimepiride is an oral blood glucose lowering drug of sulfonyl urea class.

Chemical Name

Glimepiride (1–[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea.

The CAS registry number is 93479-97-1.

Molecular formula : $C_{24}H_{34}N_4O_5S$

Molecular weight : 490.62

Structural formula:

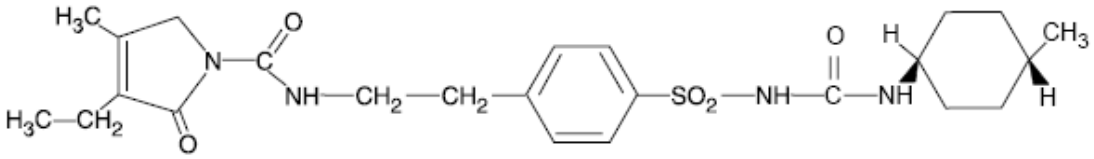


Figure 5: Structure of Glimepiride

Physical properties : Glimepiride is a white to yellowish white crystalline odorless powder.

Solubility: Glimepiride is insoluble in water, acid, base, borate and phosphate buffers but partially soluble in methanol, ethanol, acetone, and completely soluble in DMF [www.aventis.us.com].

Chemical properties: Methanolic solution of Glimepiride gives UV absorption at 229nm. [USP 31, 2008] Aqueous solution of Glimepiride gives maximum absorption between 229 and 236nm. [Anju Goyal, and I.Singhvi.2007]

Log P value : 2.5

C Log P value : 3.96 [www.tsrlinc.com]

BCS: Class 2 drug (low solubility high permeability)

Available strength: 1mg, 2mg, and 4mg

Mechanism of Action

The primary mechanism of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.

In addition extra pancreatic effect may also play a role in the activity of sulfonyl urea such as Glimepiride. This is supported by both clinical and pre-clinical studies demonstrating the Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin.

Pharmacokinetics

Absorption: After oral administration, Glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral dose in normal subjects and with multiple

oral doses in patients with Type-2 diabetes has shown significant absorption of Glimepiride with 1 hour after administration and peak drug levels at 2 to 3hours.

Distribution: After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8L (113ml/kg), and the total body clearance (Cl) was 47.8 ml/min. Protein binding was greater than 99.5%.

Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxyl methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of Glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model.

Excretion: When ^{14}C-Glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 – 90% of that recovered in the urine. Approximately 40% of that recovered in feces. No parent drug was recovered from urine or feces.

Pharmacokinetic Parameters

Table 2: Pharmacokinetic Parameters

Parameter	Single Dose
C_{max} (ng/ml)	
1 mg	103± 34 (12)
2 mg	177 ± 44 (12)
4 mg	308 ± 69 (12)
8 mg	551 ± 152 (12)
T_{max} (h)	1.4 ± 0.8 (48)
Cl/f(ml/min)	52.1 ± 16.0 (48)
Vd/f(l)	21.8 ± 13.9 (48)
$T_{1/2}$(h)	5.3 ± 4.1 (48)

CL/f=Total body clearance after oral dosing

Vd/f=Volume of distribution calculated after oral dosing

Adverse reactions

GASTRO INTESTINAL REACTIONS

Vomiting, gastro intestinal pain and diarrhoea have been reported.

DERMATOLOGIC REACTIONS

Allergic skin reactions, e.g. Pruritus, Erythema, Urticaria occurs.

HEAMATOLOGIC REACTIONS

Leukopenia, Agranulocytosis, Thrombocytopenia, Hemolytic Anemia, Aplastic Anemia, and Pancytopenia have been reported.

Indications and Usage

Glimepiride is indicated as an adjunct to diet and exercise to lower the blood glucose in patient with Type 2 diabetes mellitus. Hypoglycemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with Metformin when diet, exercise, Glimepiride or Metformin alone does not adequate glycemic control.

Dosage and Administration [Package insert of Amaryl tablets 1, 2 and 4 mg]

Usual starting dose of Glimepiride initial therapy is 1mg to 2mg once daily, administered with breakfast or first main meal.

Patient who may be more sensitive to Hypoglycemic drugs should be started at 1mg once daily, and should be titrated carefully.

The maximum starting dose of Glimepiride should not be more than 2mg. The usual maintenance dose is 1 to 4mg once daily. The maximum recommended dose is 8mg once daily.

POLYMER PROFILE

Polymer Profile

The gastro retentive formulation contains the following excipients to provide the buoyancy for the formulation.

1. Gas forming agent
2. Gel forming polymer
3. Rate controlling polymer
4. Diluent
5. Lubricant

Gas forming agent: Sodium bicarbonate [Raymond C. Rowe, et.al. 2006]

Nonproprietary Names

- BP: Sodium bicarbonate
- JP: Sodium bicarbonate
- PhEur: Natrii hydrogenocarbonas
- USP: Sodium bicarbonate

Synonyms

Baking soda; E500; *Effer-Soda*; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name and CAS Registry Number

Carbonic acid monosodium salt [144-55-8]

Empirical Formula and Molecular Weight

$NaHCO_3$, 84.01

Structural Formula

$NaHCO_3$

Functional Category

Alkalizing agent; therapeutic agent.

Applications in Pharmaceutical Formulation

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid; combinations of citric and tartaric acid are often

preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone, granules lose firmness. When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved.

Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled-release oral dosage forms of furosemide and cisapride. Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol, and improve the stability of levothyroxine.

Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

Table 3: Uses of Sodium Bicarbonate

Use	Concentration (%)
Buffer in tablets	10–40
Effervescent tablets	25–50

Incompatibilities

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.

In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt.

In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine, and levofloxacin.

Gel forming agent: Carbomer

Nonproprietary Names

- BP: Carbomers
- PhEur: Carbomera
- USPNF: Carbomer
- Note that the USPNF 23 contains several individual carbomer monographs

Synonyms

Acritamer; acrylic acid polymer; *Carbopol*; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; *Pemulen*; *Ultrez*.

Chemical Name and CAS Registry Number

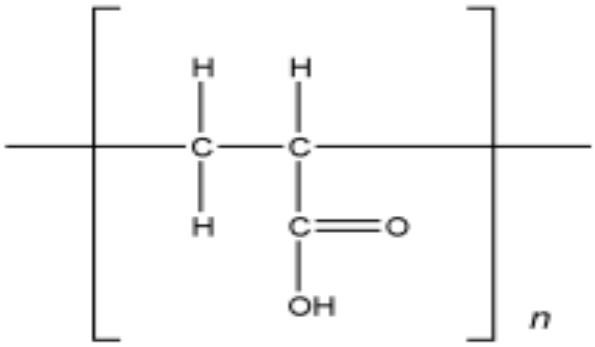
Carbomer [9003-01-4]

Note that carbomer 910, 934, 934P, 940, 941, 971P and 974P resins share the common CAS registry number 9003-01-4. Carbomer 1342 is a copolymer and has a different CAS registry number.

Molecular Weight

The molecular weight of Carbomer resins is theoretically estimated at 7×10^5 to 4×10^9. In an effort to measure the molecular weight between crosslinks, M_C, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and M_C. Estimated M_C values of 237 600 g/mol for *Carbopol 941* and of 104 400 g/mol for *Carbopol 940* have been reported. In general, carbomer resins with lower viscosity and lower rigidity will have higher M_C values. Conversely, higher-viscosity, more rigid carbomer resins will have lower M_C values.

Structural Formula



Acrylic acid monomer unit in carbomer resins.

Figure 6: Structure of Carbomer

Functional Category

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents.

Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient.

Carbomer resins have also been investigated in the preparation of sustained-release matrix beads, as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administered microspheres, in magnetic granules for site-specific drug delivery to the esophagus and in oral mucoadhesive controlled drug delivery systems.

Therapeutically, carbomer gel formulations have proved efficacious in improving symptoms of moderate-to-severe dry eye syndrome.

Table 4: Grades of Carbomers

Grade
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342

Table 5: Uses of Carbomers

Use	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	5.0–10.0

Incompatibilities

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjutants should also be avoided or used at low levels. Trace levels of iron and other transition metals can catalytically degrade carbomer dispersions. Intense heat may be generated if a carbomer is in contact with a strong basic material such as ammonia, potassium or sodium hydroxide, or strongly basic amines.

Certain amino-functional actives form water-insoluble complexes with carbomer; often this can be prevented by adjusting the solubility parameter of the fluid phase using appropriate alcohols and polyols.

Carbomers also form pH-dependent complexes with certain polymeric excipients. Adjustment of solubility parameter can also work in this situation.

Rate Controlling Polymer: Hypromellose

Nonproprietary Names

- BP: Hypromellose
- JP: Hydroxypropylmethylcellulose
- PhEur: Hypromellosum
- USP: Hypromellose

Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Molecular Weight

Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Structural Formula

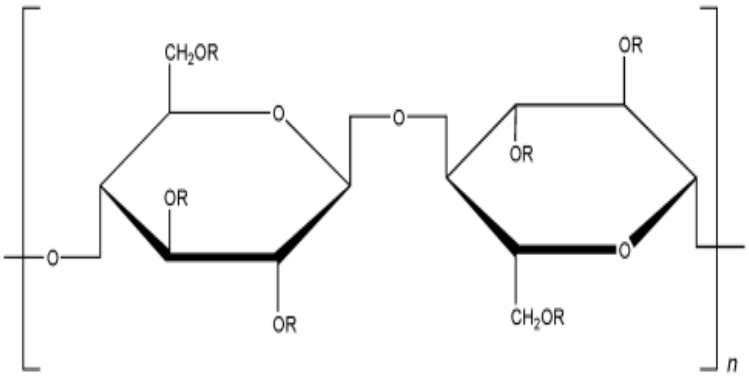


Figure 7: Structure of Hypromellose

where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Table 6: Grades of Hypromellose

***Methocel* product**	**Nominal viscosity (mPa s)**
Methocel K100 Premium LVEP	100
Methocel K4M Premium	4000
Methocel K15M Premium	15 000
Methocel K100M Premium	100 000

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Diluent: Lactose monohydrate

Nonproprietary Names

- BP: Lactose monohydrate
- PhEur: Lactosum monohydricum
- JP: Lactose
- USPNF: Lactose monohydrate

Synonyms

Lactochem, Pharmatose, HMS, NF Lactose, CapsuLac, GranuLac, PrismaLac, SacheLac, SorboLac, SpheroLac, Tablettose, Inhalac.

Chemical Name and CAS Registry Number

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}\cdot H_2O$ 360.31

Structural Formula

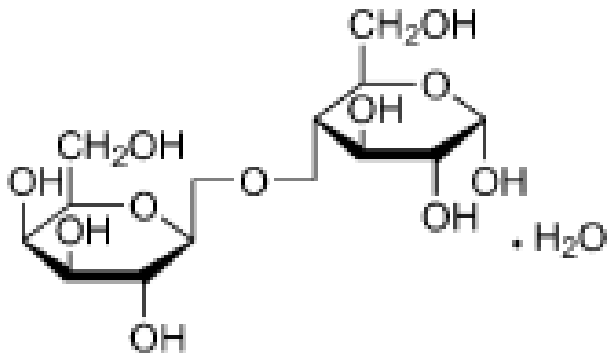


Figure 8: Structure of Lactose monohydrate

Functional Category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Applications in Pharmaceutical Formulation

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions.

Direct-compression grades of lactose monohydrate are available as granulated/ agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

Other directly compressible lactoses are spray-dried lactose and anhydrous lactose.

Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products.

Lactose is also incompatible with amino acids, aminophylline, amfetamines, and lisinopril.

Lubricant: Magnesium stearate

Nonproprietary Names

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$, 591.34

Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Incompatibilities

Incompatible with strong acids, alkalis, and, iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

EXPERIMENTAL SECTION

PART - I

ANALYTICAL METHOD USED FOR ESTIMATION OF GLIMEPIRIDE IS UV SPECTROPHOTOMETRY

Preparation of 0.1N Hydrochloric acid with 0.5% w/v of Sodium Lauryl Sulphate

8.5ml of concentrated Hydrochloric acid added in 1000ml of distilled water under stirring pH was 1.2 and 50g of Sodium Lauryl Sulphate slowly added until to complete soluble.

Standard Graph of Glimepiride in 0.1N HCL with 0.5% w/v SLS

Stock solution was prepared by 50mg of Glimepiride substance in 100ml Methanol. From this stock solution 10ml was withdrawn and diluted up to 100ml using 0.1N HCL with 0.5 % w/v SLS. Calibration curve was prepared by using different concentration (5µg/ml - 25µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 236 nm. [Anju Goyal and I. Singhvi, 2007] and are as given in Table 7.

RESULTS AND DISCUSSION

The absorbance for various concentrations measured at 236nm is as follows

Table 7: Standard Graph of Glimepiride in 0.1N HCL with 0.5% w/v SLS

Sl. No.	Concentration (µg/ml)	Absorbance at 236nm
1	5	0.2531
2	10	0.4473
3	15	0.6205
4	20	0.8057
5	25	1.0412

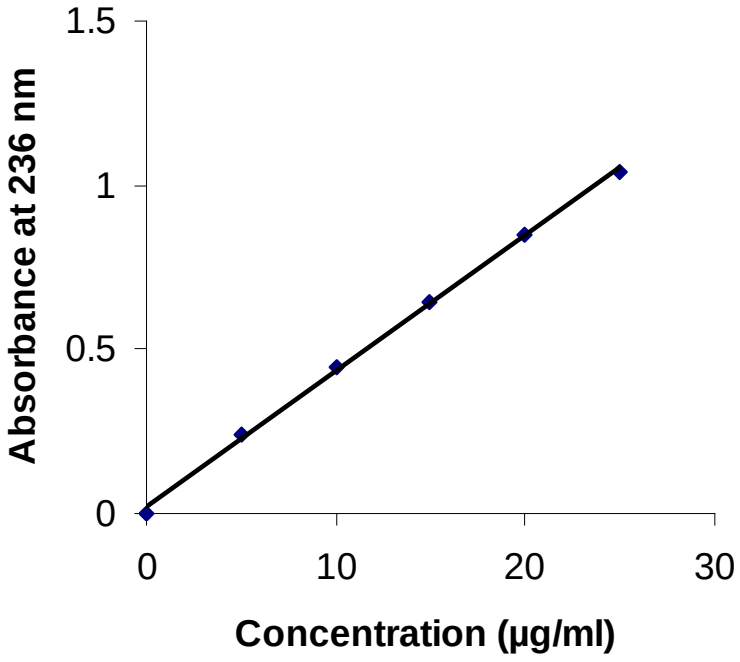


Figure 9: Standard Graph of Glimepiride in 0.1N HCL with 0.5% w/v SLS

Abs = A + B * Conc

A = 0.0050

B = 0.0318

Coefficient 0.999862

Glimepiride shows good linearity with the range 5 to 25µg with r^2 = 0.9998, Slope = 0.318, Intercept = 0.0050.

PART-II

PRE FORMULATION STUDIES

Drug Polymer Interaction Studies

IR Spectroscopy (using IR Spectrophotometer Jasco FT-IR8201 PC by KBr Pellet Method) was carried out on pure substances and their physical mixtures to search the possible interaction (Glimepiride) [Y.R. Sharma, 2007] and various polymers are depicted in figure 10 to 13.

RESULTS AND DISCUSSION

IR Spectra of Pure Drug

The IR Spectrum for Glimepiride in pure form was observed to have peaks at [Pyrrole] 3475 cm^{-1} [C = O] 1670 cm^{-1} [C – N] 1443 cm^{-1} [N - H] 3417 cm^{-1} [SO_2] 1151 cm^{-1} [N - H] 3285 cm^{-1} which are shown in figure 10.

IR Spectra of Physical Mixture of Glimepiride with Hypromellose [K4MCR]

The IR Spectra of Glimepiride with HPMC [K4MCR] was observed to have peaks at 3261 cm^{-1}, 1387 cm^{-1}, 1583 cm^{-1}, 3265 cm^{-1}, 1303 cm^{-1}, 3513 cm^{-1} which are shown in figure 11, which indicates that there is no interaction between two.

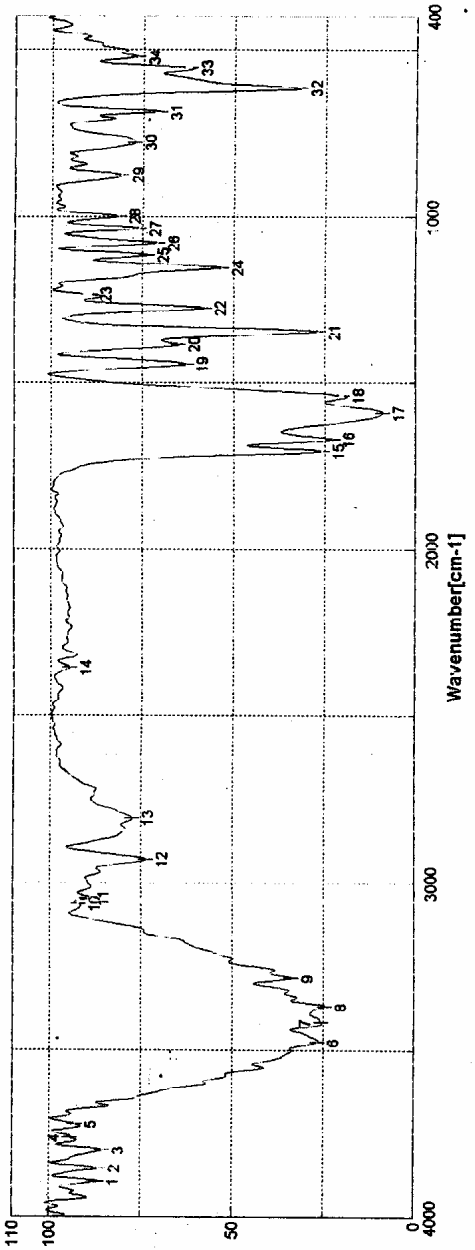
IR Spectra of Physical Mixture of Glimepiride with Carbopol

The IR Spectra of Glimepiride with Carbopol was observed to have peaks at 3373 cm^{-1}, 1739 cm^{-1}, 1455 cm^{-1}, 3277 cm^{-1}, 1111 cm^{-1}, 3217 cm^{-1} which are shown in figure 12, which indicates that there is no interaction between two.

IR Spectra of Physical Mixture of Glimepiride with Hypromellose [K100MCR]

The IR Spectra of Glimepiride with Hypromellose K100MCR was observed to have peaks at 3503 cm^{-1}, 1644 cm^{-1}, 1445 cm^{-1}, 3676 cm^{-1}, 1124 cm^{-1}, 3157 cm^{-1} which are shown in figure 13, which indicates that there is no interaction between two.

Figure 10: IR Spectra of pure drug



Accumulation	40		Resolution	4 cm-1			
Zero Filling	ON		Apodization	Cosine			
Gain	8		Scanning Speed	2 mm/sec			
Date/Time	10/29/2008 0:58PM		Update	10/30/2008 11:39AM			
Operator	C.Geetha						
File Name	Pure drug						
Sample Name	pure drug						
Comment							

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3895.5	86.7258	2	3855.97	86.3381	3	3801.01	85.3281	4	3764.37	84.2762	5	3723.87	92.823
6	3475.1	26.6238	7	3417.24	25.7137	8	3369.03	24.5265	9	3285.14	33.7821	10	3085.3	92.1441
11	3047.94	88.6521	12	2929.34	73.8423	13	2806.88	77.426	14	2353.68	84.7893	15	1704.76	25.577
16	1670.05	22.6862	17	1589.06	9.13578	18	1538.92	20.1042	19	1443.46	62.9165	20	1383.68	65.1505
21	1346.07	26.6577	22	1272.79	57.9439	23	1232.29	89.2895	24	1151.29	53.2212	25	1113.69	73.6525
26	1078.88	70.7579	27	1034.62	75.7824	28	987.962	81.5845	29	876.488	80.7315	30	778.136	77.1721
31	686.534	70.3142	32	615.181	31.8302	33	555.398	62.0715	34	520.686	78.5492			

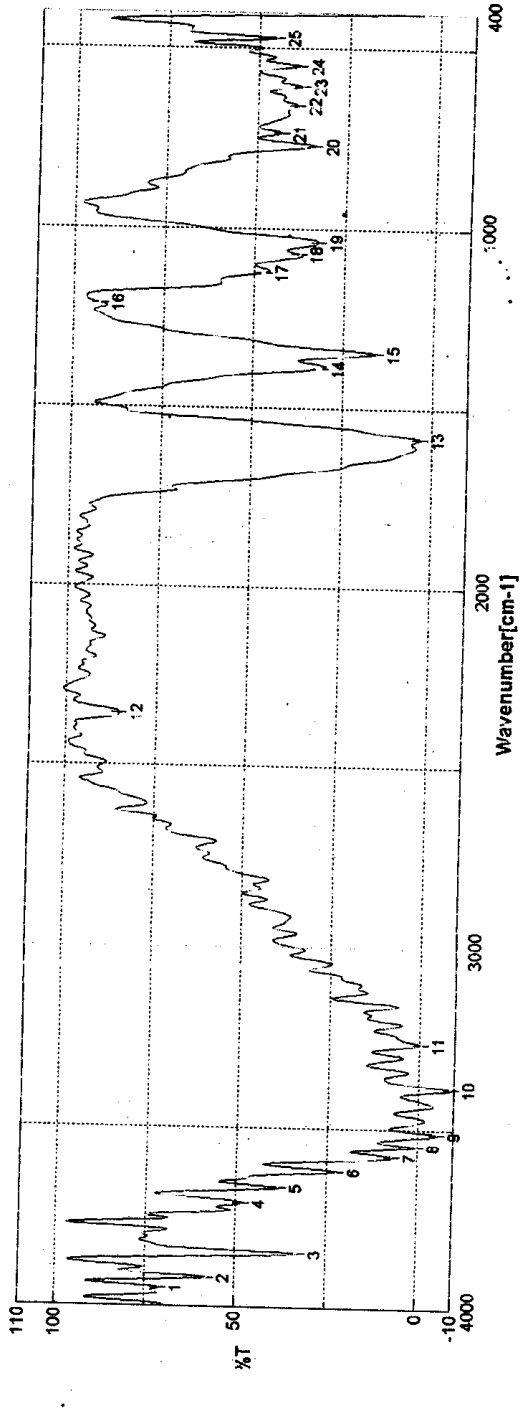


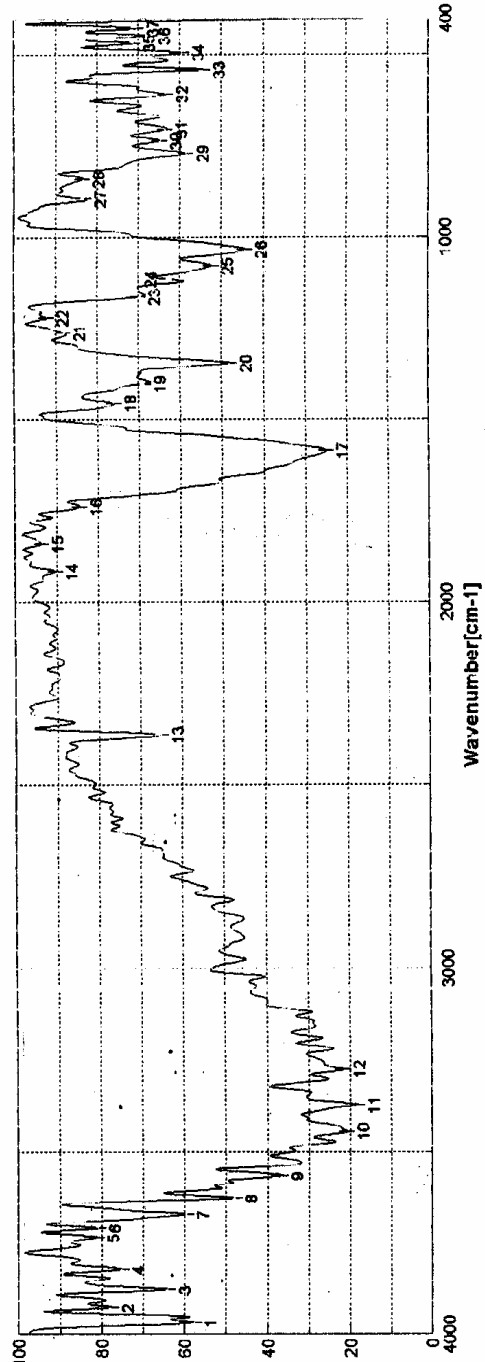
Figure 11: IR Spectra of pure drug and HPMC K4MCR

Accumulation	40
Zero Filling	ON
Gain	64
Date/Time	10/29/2008 1:46PM
Operator	C.Geetha
File Name	F3
Sample Name	F3
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	10/30/2008 11:07AM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3949.5	70.8934	2	3919.61	57.9691	3	3852.11	32.8017	4	3712.3	48.4577	5	3668.91	38.2893
6	3621.66	22.3186	7	3578.27	6.91784	8	3549.34	0.474372	9	3513.67	-5.435	10	3388.32	-9.17207
11	3285.86	-0.393347	12	2351.77	85.1585	13	1583.27	3.11809	14	1387.53	31.0993	15	1346.07	15.6527
16	1210.11	92.5353	17	1120.44	47.2253	18	1067.41	37.6234	19	1033.86	32.2372	20	768.494	33.9041
21	733.782	43.2191	22	658.571	39.0009	23	605.539	37.7478	24	547.685	38.6196	25	471.51	45.2443

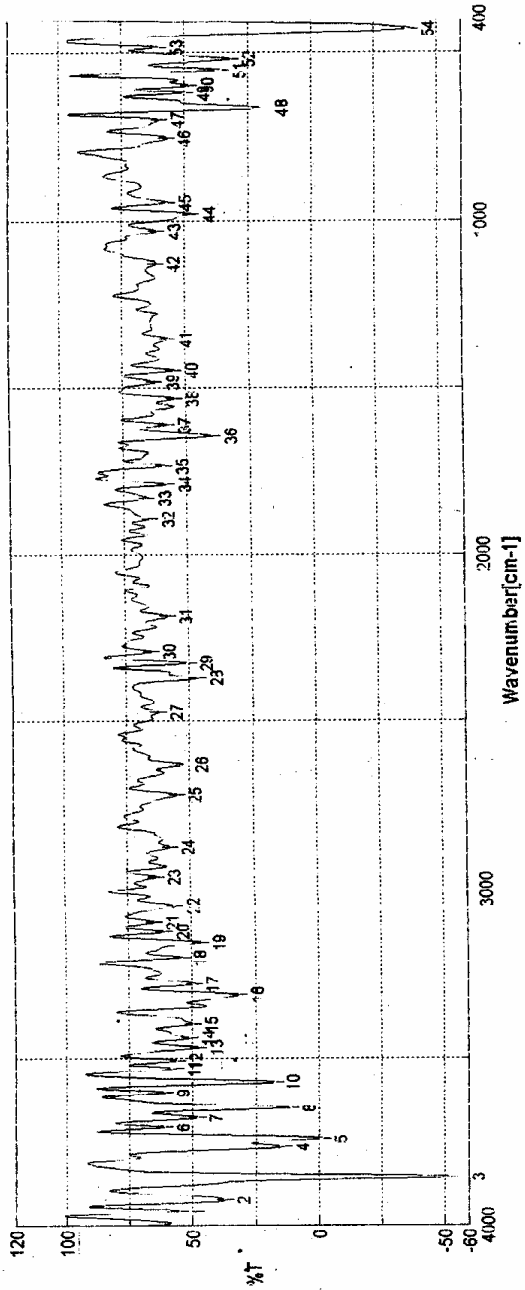
Figure 12: IR Spectra of pure drug and Carbopol



Accumulation	40	Resolution	4 cm-1		
Zero Filling	ON	Apodization	Cosine		
Gain	32	Scanning Speed	2 mm/sec		
Date/Time	10/29/2008 1:44PM	Update	10/30/2008 11:10AM		
Operator	C.Geetha				
File Name	F4				
Sample Name	F4				
Comment					

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3968.78	57.7412	2	3926.36	77.5712	3	3878.15	63.9956	4	3822.22	75.1768	5	3736.4	81.1951
6	3710.37	80.699	7	3672.77	59.8018	8	3628.41	47.8515	9	3563.81	36.8742	10	3445.21	20.6808
11	3373.85	18.0227	12	3277.43	21.5378	13	2362.37	65.1104	14	1917.86	90.4638	15	1841.69	93.704
16	1739.48	84.5379	17	1586.16	24.9369	18	1455.03	76.0499	19	1401.03	68.7371	20	1346.07	48.1034
21	1259.28	88.221	22	1218.79	92.17	23	1160.94	70.0124	24	1111.76	83.1029	25	1076.08	52.528
26	1031.73	44.393	27	893.844	83.2479	28	840.812	83.5821	29	769.458	58.4874	30	733.782	64.8524
31	702.926	63.5908	32	608.431	63.4317	33	540.935	54.516	34	493.688	58.4546	35	466.689	71.4048
36	448.44	67.8679	37	425.227	70.4962									

Figure 13: IR Spectra of pure drug and HPMC K1000MCR



Accumulation 40
Zero Filling ON
Gain 64
Date/Time 12/12/2008 2:16PM
Operator C.Geetha
File Name 7
Sample Name 7
Comment

Resolution 4 cm-1
Apodization Cosine
Scanning Speed 2 mm/sec
Update 12/12/2008 2:19PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3955.28	54.8002	2	3923.47	36.8704	3	3855.01	-58.3783	4	3764.37	13.6133
6	3706.51	60.6974	7	3676.62	47.9281	8	3648.66	10.9274	9	3602.38	60.7496
11	3530.06	56.2915	12	3506.92	55.67	13	3467.38	47.3174	14	3439.42	50.8269
16	3313.11	3 .3064	17	3280.32	48.7753	18	3203.18	53.8831	19	3157.86	45.9817
21	3095.19	64.5978	22	3047.94	56.1284	23	2960.2	63.3593	24	2871.49	57.8818
26	2829.46	52.0707	27	2475.19	62.0375	28	2369.12	46.1024	29	2323.8	50.2416
31	2183.02	58.1248	32	1891.83	64.5036	33	1831.08	65.7604	34	1789.62	57.6868
36	1644.96	39.5126	37	1611.23	57.6269	38	1532.17	54.2941	39	1482.03	62.0199
41	1352.82	56.7253	42	1124.3	61.2905	43	1027.87	60.9804	44	976.768	47.3368
46	753.066	58.9563	47	699.069	59.8057	48	665.321	18.6712	49	620.966	49.6294
51	551.542	35.2084	52	519.722	31.3436	53	483.081	60.1919	54	430.048	-39.7337

No.	cm-1	%T
5	3740.26	-1.63903
10	3570.56	17.0558
15	3397.96	49.6175
20	3125.08	60.5609
25	2718.17	54.8341
30	2289.09	64.614
35	1734.66	58.7651
40	1445.39	54.5178
45	943.02	56.6725
50	597.825	47.6905

PART - III

Formulation Development

Direct compressible blend was prepared by using Glimepiride, Lactose monohydrate, Hypromellose, Carbopol, and Magnesium stearate along with Sodium bicarbonate. This compressible mixture were mixed thoroughly and sifted through 30 mesh. This compressible blend was then compressed as a tablet by using 7mm punch weighing 150 mg.

Various formulations were compressed by varying the proportion of rate controlling polymer (Hypromellose - K4MCR / K100MCR), gel forming polymer (Carbopol), as depicted in Table 8.

Table 8: Composition of tablet formulations

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**
Glimepiride	4	4	4	4	4	4	4
Lactose monohydrate	75	65.5	55	65.5	55	35	75
Sodium bicarbonate	50	50	50	50	50	50	50
Hypromellose K4MCR	10	19.5	30	10	10	30	--
Hypromellose K100MCR	--	--	--	--	--	--	10
Carbopol 934P	10	10	10	19.5	30	30	10
Magnesium stearate	1	1	1	1	1	1	1
Tablet weight	150	150	150	150	150	150	150
% of Gel forming Polymer	**7**	**7**	**7**	**13**	**20**	**20**	**7**
% of Rate controlling polymer	**7**	**13**	**20**	**7**	**7**	**20**	**7**

PART - IV

Evaluation of Granules

A) Angle of Repose

Flow properties of the granules were evaluated by determining the Angle of Repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing core method of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its top a given height (1 cm), h, above graph paper placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, with R being the radius of the base of the granules conical pile and the angle of repose was calculated by using the equation [Cooper. J and Gunn L., 1986] and are as reported in Table 9.

$$\tan \theta = h/r$$

where θ is the angle of repose.

B) Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until

no further change in volume was noted. LBD and TBD were calculated using the following formula [Shah, et.al. 1999] and are as reported in Table 10.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

C) Compressibility Index

Compressibility index of the powder was determined by Carr's compressibility index [Aulton ME, and Wells, 1988] and are as reported in Table 10.

Carr's index (%) = [(TBD – LBD) x 100]/TBD.

RESULTS AND DISCUSSION

A) Angle of Repose

The angle of repose for the granules of various formulations F1 to F7 are as given in Table 9.

Table 9: Angle of Repose of granules

Formulation (n)	Angle of Repose (θ)
F1	23°.62′
F2	20°.92′
F3	20°.22′
F4	21°.03′
F5	23°.38′
F6	25°.34′
F7	25°.97′

Angle of Repose of our precompressed granules was in the range 20º.22′ to 25º.97′, which indicate that precompressed granules having excellent flow property which is in compliance with the angle of repose ≤ 30º as mentioned in the Leon Lachman, et.al. 1990.

B) Bulk Density

The LBD and TBD, Compressibility index for the granules for various formulations F1 to F7 are given in Table 10.

Table 10: Bulk Density and Compressibility index of Granules

Formulation (n)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility index (%)
F1	0.482	0.614	21.50
F2	0.451	0.603	25.21
F3	0.457	0.614	25.57
F4	0.468	0.598	21.74
F5	0.462	0.582	20.62
F6	0.453	0.543	16.57
F7	0.442	0.567	22.05

LBD and TBD for all the formulations ranged from 0.442 to 0.482 and 0.543 to 0.614 respectively. Compressibility Index (%) ranged from 16.57 to 25.57. All the formulations exhibited good compressibility index.

EVALUATION OF COMPRESSED TABLETS

Quality control test for Glimepiride compressed tablets (GFDDS) were performed as follows.

1. General Appearance

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance for monitoring the production process.

Size and shape

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process.

2. Thickness and diameter

Ten tablets were measured using vernier caliper. Ten tablets from each formulation were used and average value was calculated and as are given in Table 11.

3. Hardness

From each batch five tablets were tested using Monsanto Hardness Tester and as are given in Table 12.

4. Friability

The friability test was performed for all the formulated tablets using Roche Friabilator. Ten tablets were taken and their weight was determined (W_0) then they were placed in a rotating drum. Then they were subjected to 100 revolutions. After completion of 100 revolutions or 4 min of time at 25 rpm, the tablets were again

weighed (W). The percentage friability (f) was calculated by the formula given and as are given in Table 13.

$$f = W_0 - W / W_0 \times 100$$

5. Weight variation

For uniformity of weight, twenty tablets from each formulation were selected at random. The individual 20 tablets from each batch were determined by using electrical balance and as are shown in Table 14.

6. Content Uniformity

Each tablet was crushed and transferred to 100 ml volumetric flask. The powder was dissolved in 3 ml of methanol and volume made up to 100 ml by 0.1N HCL with 0.5% w/v of SLS. The sample solution kept under stirring for 5 minutes after that it was filtered through Whatman filter paper. Appropriate dilution of filtered solution was done by 0.1N HCL and with 0.5% w/v of SLS. Absorbance of solution is measured at 236 nm by UV Spectrophotometer (BP 2003)and as are shown in Table 15.

7. Assay

Weigh and powdered 10 tablets. Weigh accurately a quantity of powder equivalent to about 1.5 gm and shake with 100 ml of methanol for 10 minutes. From that 10ml taken and diluted up to 100 ml using 0.1N HCL with 0.5% w/v of SLS. The sample solution kept under stirring for 5 minutes after that it was filtered through Whatman filter paper. Appropriate dilution of filtered solution was done by 0.1N

HCL and with 0.5% w/v of SLS. Absorbance of solution is measured at 236nm by UV Spectrophotometer and as are shown in Table 16.

8. In vitro Dissolution Studies

Dissolution profile was performed using the media containing 0.1N HCL with 0.5% w/v of Sodium Lauryl Sulphate (SLS). This dissolution test was carried out by using USP Apparatus-1 (basket) at 50 rpm, temperature at 37 ± 0.5ºC. 5ml of sample was withdrawn and equal volume of dissolution media was replaced at a definite intervals and the concentration of drug present in the sample is estimated using UV Spectroscopy as mentioned earlier in Part-I.

The drug release profile for various formulations from F1 to F7 and for the marketed sample are as reported below.

Drug Release Kinetics

Method used to compare dissolution data was,

• Model Dependent Methods in which the dissolution profile of each formulation has been subjected various kinetics like zero order, first order, Higuchi's, Korsmeyer's [Saathoff N, et.al. 1992; Wai-Yip Lee T, et.al. 2000]

The data obtained from in vitro drug release studies were plotted in various kinetic models: as mentioned below zero order (Equation 1) as cumulative amount of drug released vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \qquad \text{(Equation 1)}$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$LogC = LogC_o - kt/2.303 \qquad \text{(Equation 2)}$$

where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

$$Q = Kt^{½} \qquad \text{(Equation 3)}$$

where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time. Drug release were plotted in Korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$M_t/M_\infty = Kt^n \qquad \text{(Equation 4)}$$

where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant[Hamid A. Merchant, et.al. 2006] and as are shown in figure 16 to 43.

9) Buoyancy test

Buoyancy test was carried out in dissolution media [Timmermans and Andre, 1994] up to 8 hours.

RESULTS AND DISCUSSION

1) General Appearance

The shape of the tablets of all formulation remained circular with no visible cracks.

2) Thickness and Diameter

The thickness and diameter for the compressed tablets of various formulations F1 to F7 are as given in Table 11.

Table 11: Diameter and Thickness of Compressed Tablet

Formulations	Diameter (mm) *	Thickness (mm) *
F1	7.05	2.6 ± 0.02
F2	7.02	2.7 ± 0.03
F3	7.03	2.5 ± 0.04
F4	7.05	2.9 ± 0.01
F5	7.00	2.6 ± 0.03
F6	7.01	2.6 ± 0.02
F7	7.02	2.9 ± 0.02

***** - Average value of 10 tablets

All the formulations showed thickness in range of 2.5mm to 2.9mm.

All the formulations showed diameter in range of 7.01mm to 7.05mm which is shown in Table 11.

3) Hardness

The hardness test of various formulations F1 to F7 are as given in Table 12.

Table 12: Hardness of Compressed Tablet

Formulations	Hardness Kg/Cm^2
F1	4.7
F2	4.7
F3	4.8
F4	4.7
F5	4.7
F6	4.2
F7	4.5

All the formulations showed reasonably good hardness value of 4.2 to 4.8 kg/cm^2 is given in Table 12.

4) Friability

The friability test of various formulations F1 to F7 are as given in Table 13.

Table 13: Friability of Compressed Tablets

Formulations	Friability (%)
F1	0.052
F2	0.041
F3	0.040
F4	0.032
F5	0.021
F6	0.011
F7	0.012

Compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. [Leon Lachman, et.al. 1990] This indicates that the tablets can withstand the mechanical shocks reasonably well during handling which are shown in Table 13.

5) Weight Variation

The weight variation test of various formulations F1 to F7 are as given in Table 14.

Table 14: Weight variation of Compressed Tablets

Formulations	Weight Variation (mg) *
F1	149.58 ± 0.81
F2	149.99 ± 0.83
F3	151.01 ± 0.73
F4	150.08 ± 0.72
F5	150.05 ± 0.80
F6	150.00 ± 0.20
F7	150.32 ± 0.71

***** - Average value of 20 tablets.

The percentage deviation allowed for a tablet weighing more than 80 mg and less than 250 mg ± 7.5% as mentioned in BP 2003.

The percentage deviation obtained from the various formulations was observed within the pharacopoeial limit.

6) Content Uniformity

The content uniformity test of various formulations F1 to F7 are given in Table 15.

Table 15: Content uniformity of Compressed tablets

Formulations	Amount of drug content (%)
F1	101.32
F2	98.60
F3	99.01
F4	102.13
F5	108.07
F6	101.52
F7	99.33

Content uniformity test revealed that of tablets within the range (80% to 120%) of pharmacopeial (BP 2003) limit which are shown in the Table 15.

7) Assay

The assay of various formulations F1 to F7 are as given in Table 16.

Table 16: Assay of Compressed tablets

Formulations	Assay (%)
F1	92.70
F2	93.89
F3	101.30
F4	94.00
F5	99.06
F6	91.32
F7	95.64

The assay revealed that of tablets within the range (95% to 105%) of which are shown in the Table 16.

8. Dissolution

***In vitro* dissolution studies of various formulations and marketed sample.**

The dissolution profile of various formulations F1 to F7 and marketed formulations are as mentioned below in Table 17 and 18 as depicted in Figure 14 and 15 respectively.

Table 17: *In vitro* drug release profile data of various formulations

Time in Hrs	Percentage of Drug Released						
	F1	F2	F3	F4	F5	F6	F7
1	32	30	27	17	16	31	19
2	57	37	45	23	17	56	36
3	75	50	66	27	21	75	46
4	93	68	91	33	23	92	53
5	97	92	93	33	27	97	76
6	--	--	--	38	28	--	79
7	--	--	--	45	33	--	85
8	--	--	--	53	54	--	89

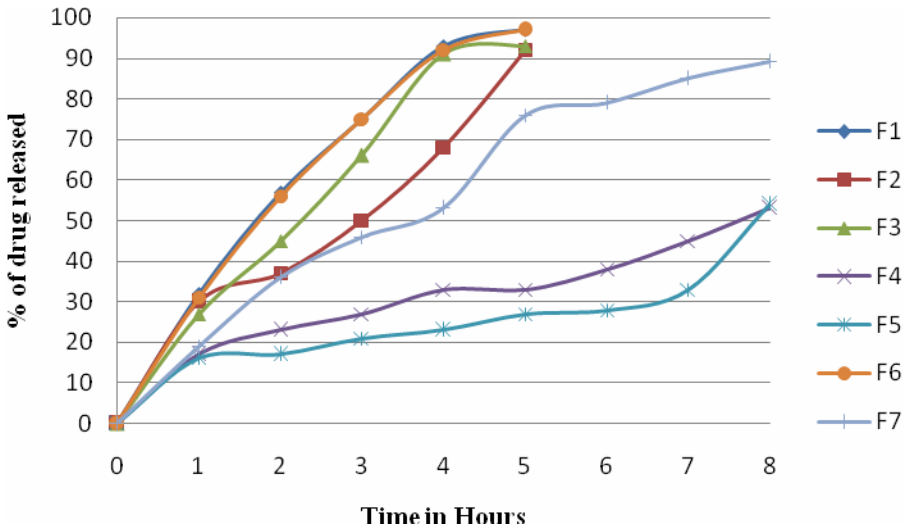


Figure 14: *In vitro* drug release profile data of various formulations

In various formulations 92 to 97% of release was observed by the formulations F1, F2, F3, and F6 within 5 hours. 89% of release was observed by the formulation F7 up to 8 hours, 52 to 55% of release observed by the formulations F4 and F5 up to 8 hours.

In vitro drug release profile of Marketed Formulation

Table 18: Drug release profile for Marketed Formulation

Time in minutes	% of drug released
15	54
30	80
45	96

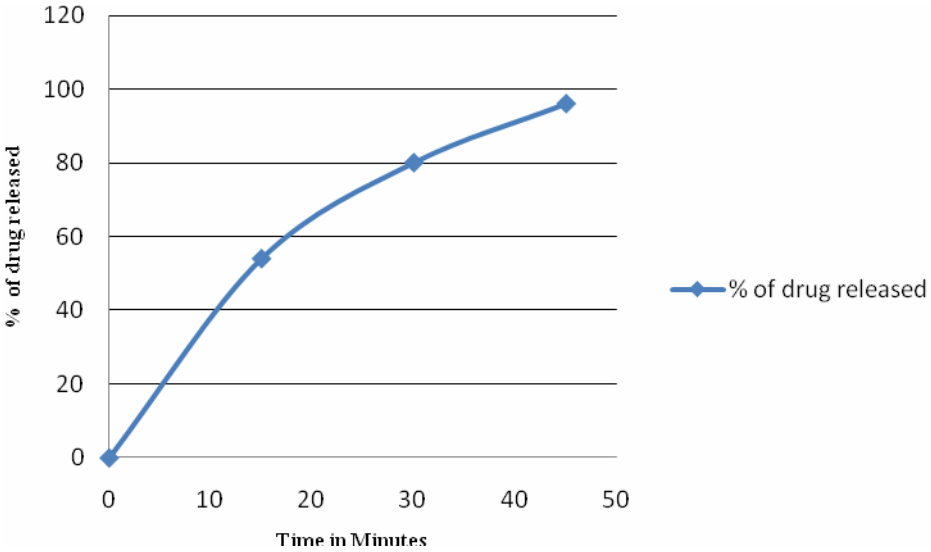


Figure 15: *In vitro* drug release profile of Marketed Formulation

In marketed preparation 96% of release was observed within 45 minutes.

Dissolution Kinetics

Dissolution Kinetics for Formulation 1 (F1)

The dissolution profile of formulation F1 was subjected to various kinetic studies and are as depicted in the following figures 16 to 19.

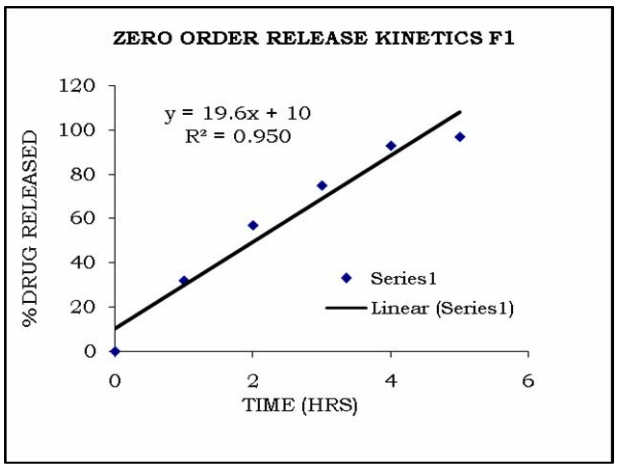


Figure 16: Zero order release kinetics F1

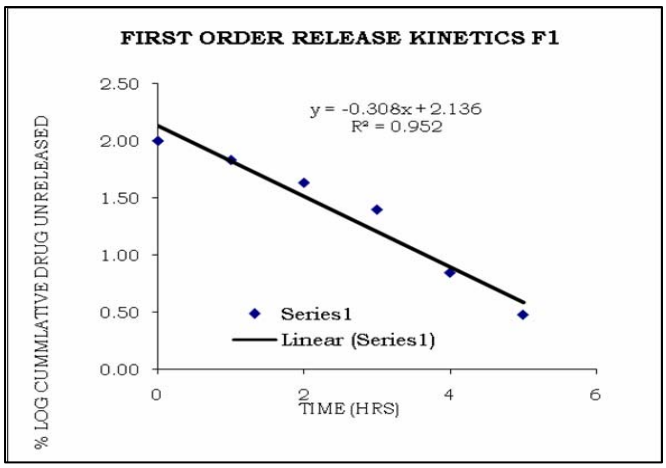


Figure 17: First order release kinetics F1

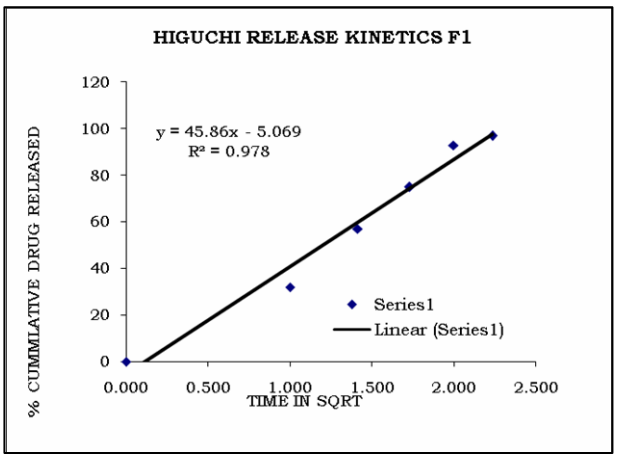


Figure 18: Higuchi release kinetics F1

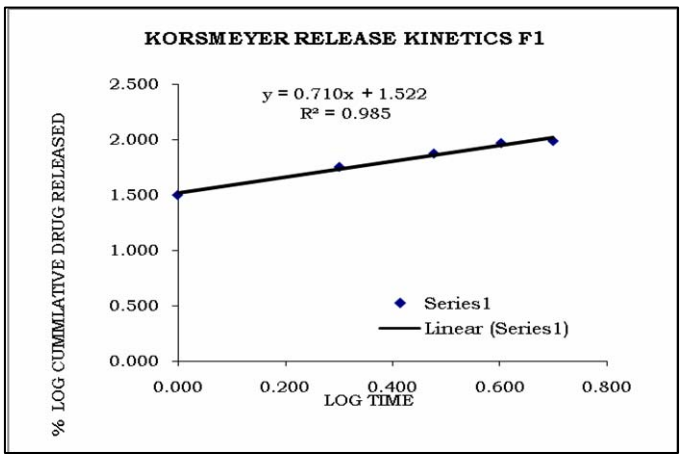


Figure19: Korsmeyer release kinetics F1

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F1 was found to obey Korsmeyer's release kinetics.

Dissolution Kinetics for Formulation 2 (F2)

The dissolution profile of formulation F2 was subjected to various kinetic studies and are as depicted in the following figures 20 to 23.

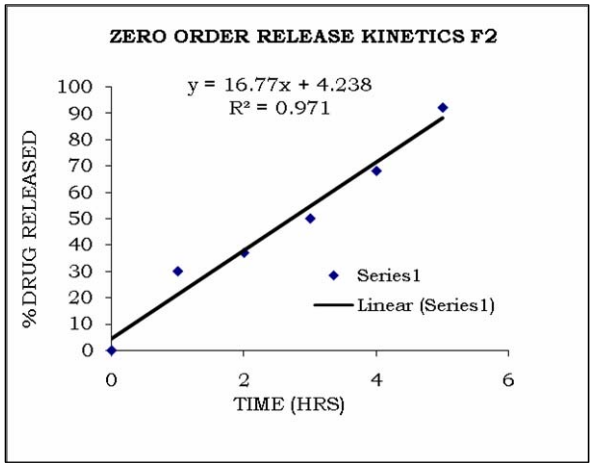


Figure 20: Zero order release kinetics F2

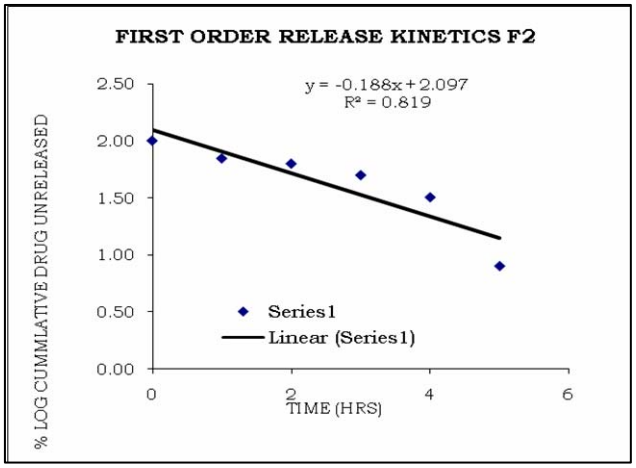
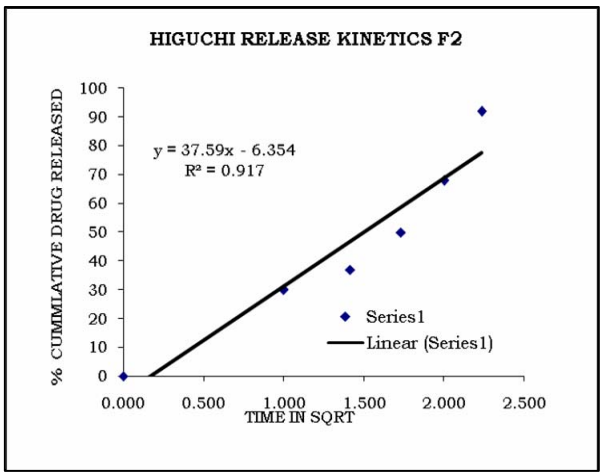


Figure 21: First order release kinetics



FFigure 22: Higuchi release kinetics F2

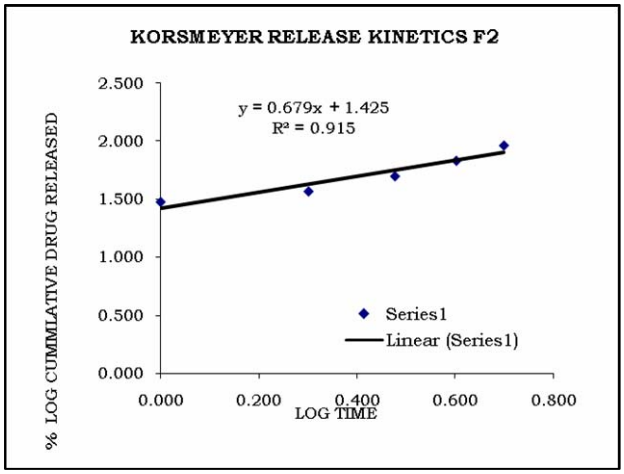


Figure 23: Korsmeyer release kinetics F2

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F2 was found to obey Zero order release kinetics.

Dissolution Kinetics for Formulation 3 (F3) The dissolution profile of formulation F3 was subjected to various kinetic studies and are as depicted in the following figures 24 to 27.

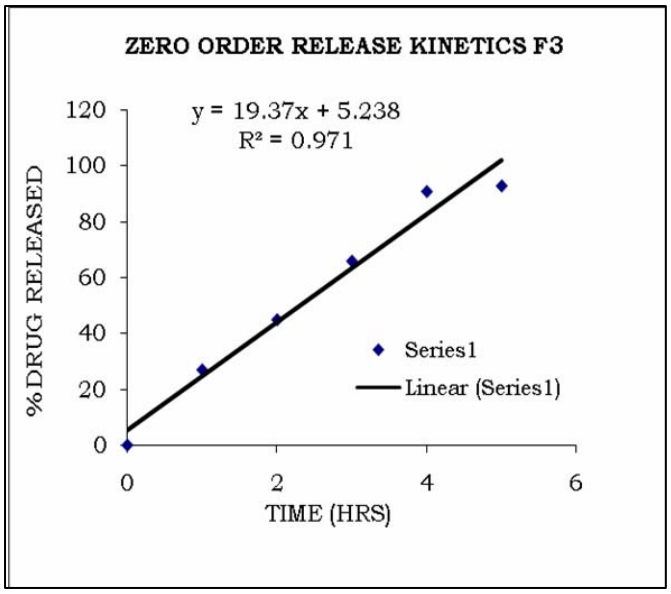


Figure 24: Zero order release kinetics F3

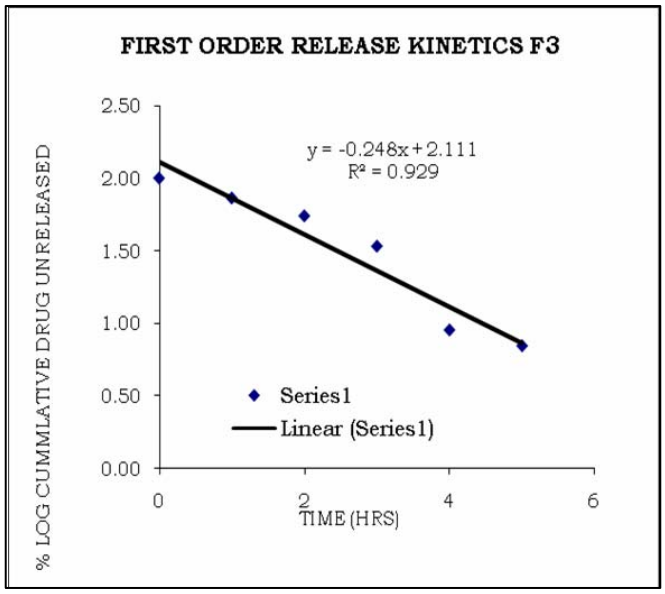


Figure 25: First order release kinetics F3

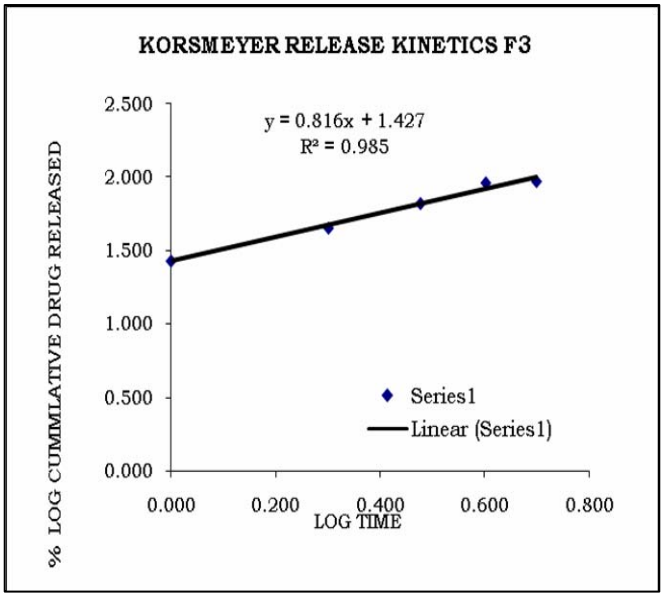


Figure 26: Higuchi release kinetics F3

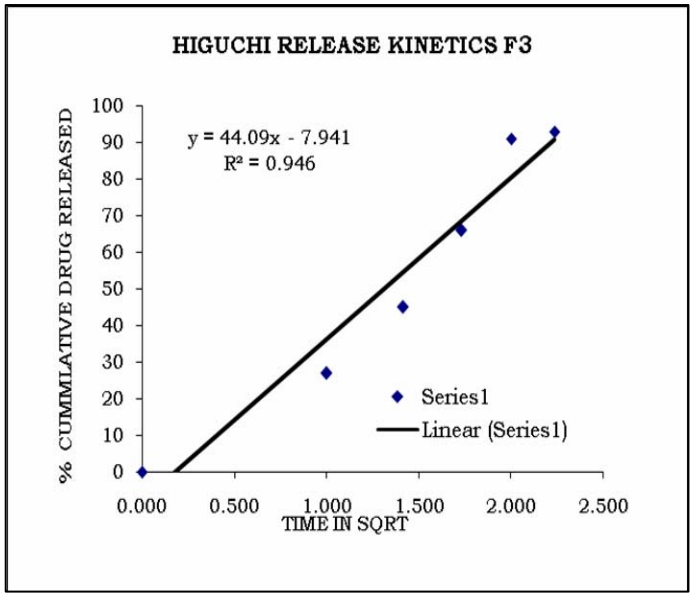
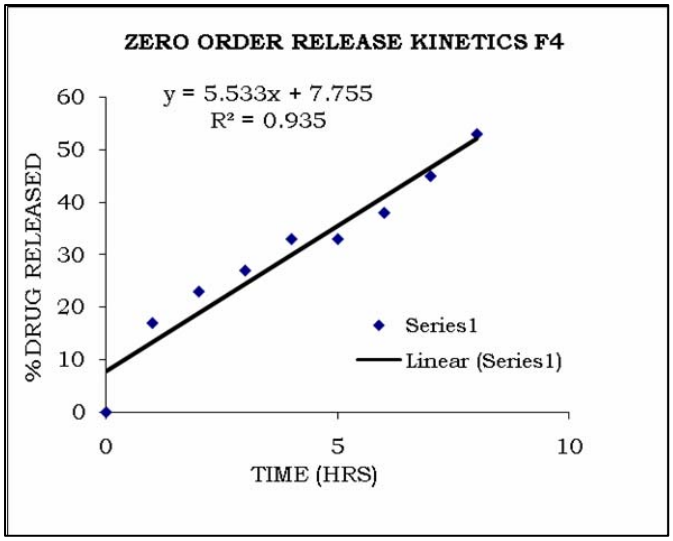


Figure 27: Korsmeyer release kinetics F3

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F3 was found to obey Korsmeyer's order release kinetics.

Dissolution Kinetics for Formulation 4 (F4)

The dissolution profile of formulation F4 was subjected to various kinetic studies and are as depicted in the following figures 28 to 31



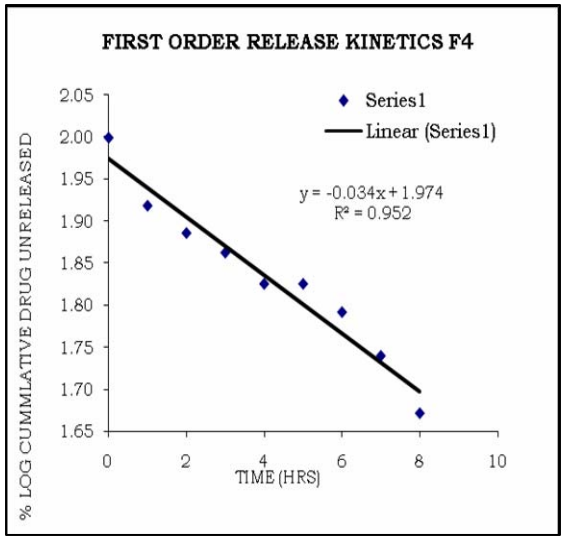
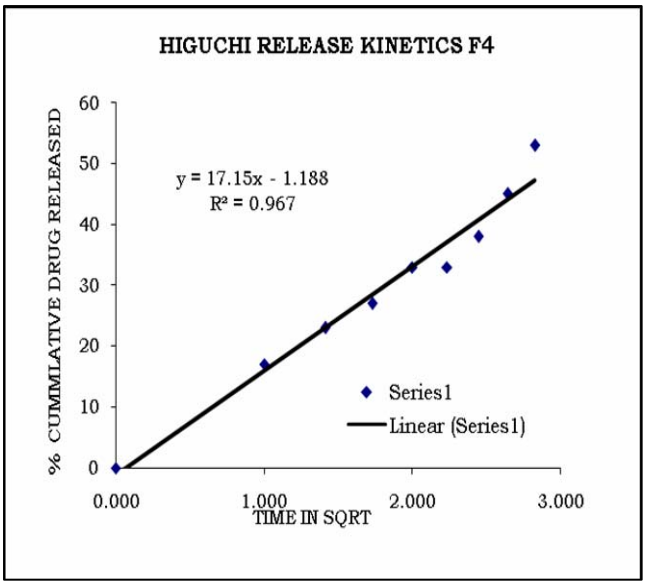


Figure 28: Zero order release kinetics F4

Figure 29: First order release kinetics F4



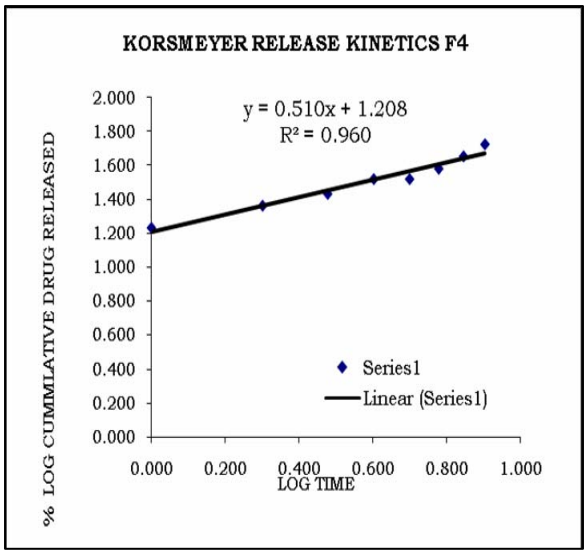


Figure 30: Higuchi release kinetics F4

Figure 31: Korsmeyer release kinetics F4

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F4 was found to obey Higuchi release kinetics.

Dissolution Kinetics for Formulation 5 (F5)

The dissolution profile of formulation F5 was subjected to various kinetic studies and are as depicted in the following figures 32 to 35.

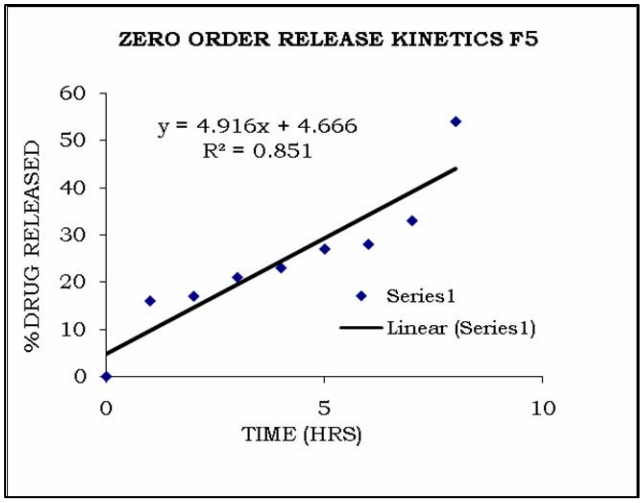


Figure 32: Zero order release kinetics F5

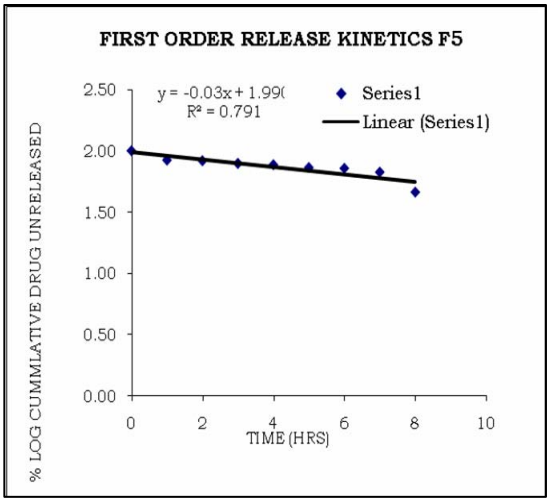


Figure 33: First order release kinetics F5

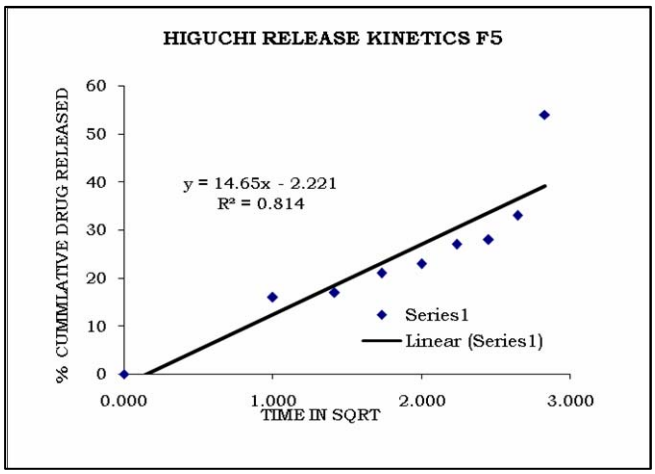


Figure 34: Higuchi release kinetics F5

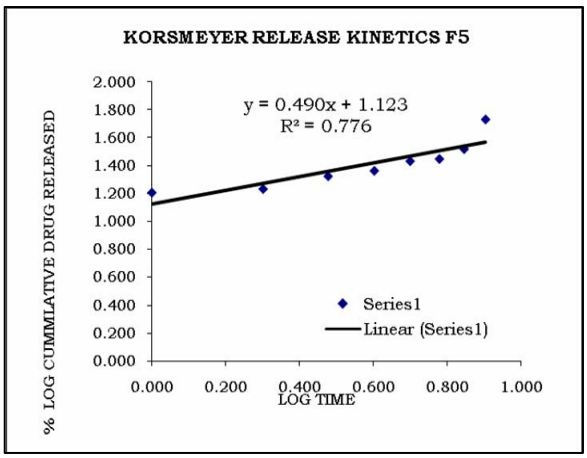


Figure 35: Korsmeyer release kinetics F5

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F5 was found to obey Zero order release kinetics.

Dissolution Kinetics for Formulation 6 (F6)

The dissolution profile of formulation F6 was subjected to various kinetic studies and are as depicted in the following figures36 to 39.

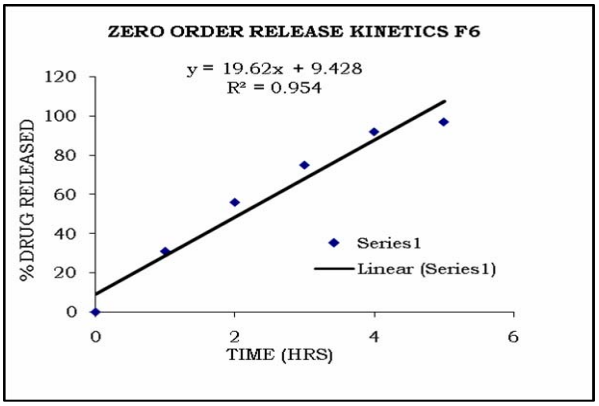


Figure 36: Zero order release kinetics F6

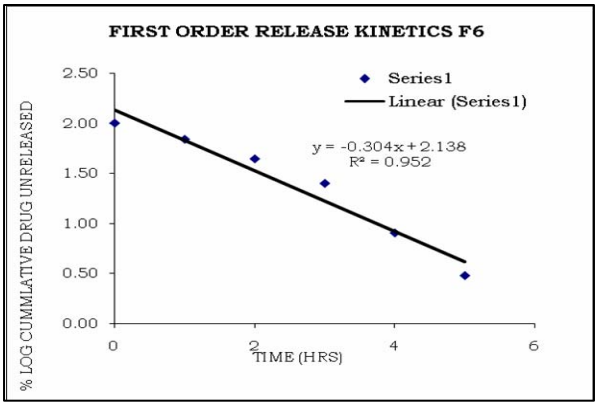


Figure 37: First order release kinetics F6

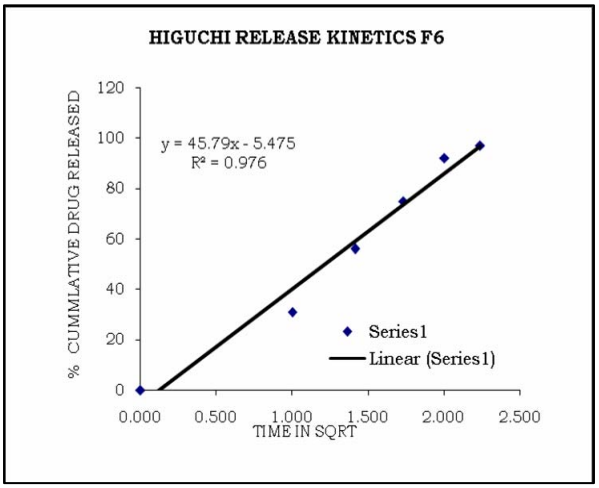


Figure 38: Higuchi release kinetics F6

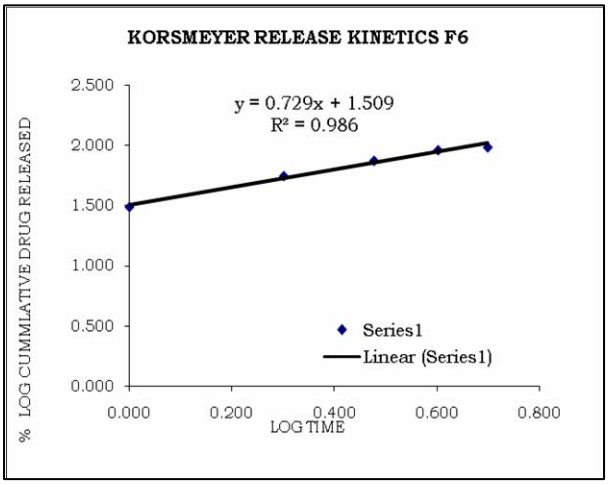


Figure 39: Korsmeyer release kinetics F6

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F6 was found to obey Korsmeyer's release kinetics.

Dissolution Kinetics for Formulation 7 (F7)

The dissolution profile of formulation F7 was subjected to various kinetic studies and are as depicted in the following figures 40 to 43.

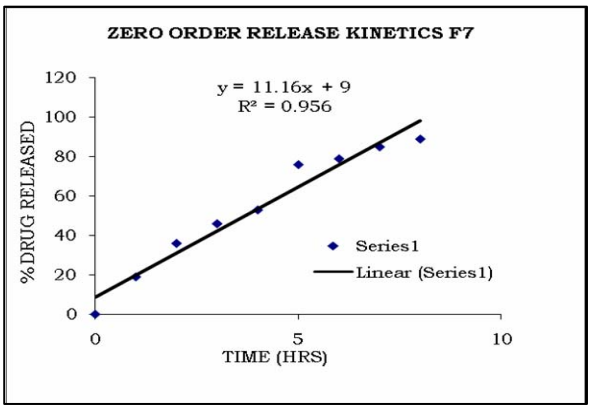


Figure 40: Zero order release kinetics F7

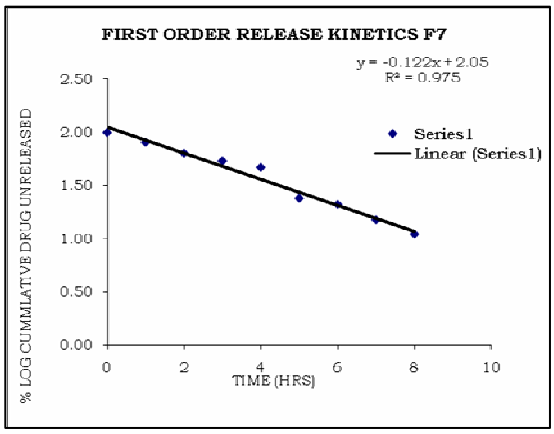


Figure 41: First order release kinetics F7

The release profile exhibiting a maximum 'r^2' value was found to obey that particular kinetics. Hence F7 was found to obey Korsmeyer's release kinetics.

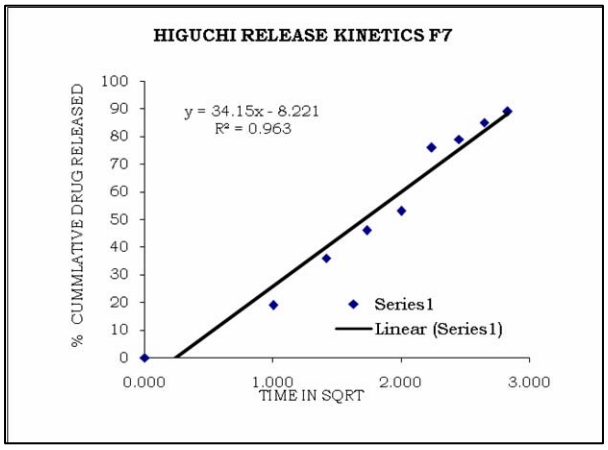


Figure 42: Higuchi release kinetics F7

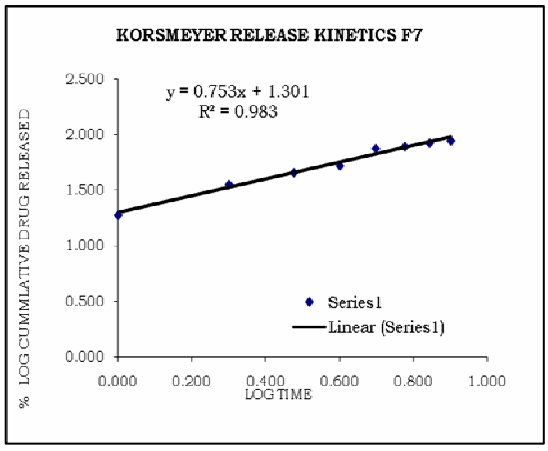


Figure 43: Korsmeyer release kinetics F7

The release profile of all the formulation, F1 was found to obey Korsmeyer's release kinetics, F2 was found to obey Zero order release kinetics, F3 was found to obey Korsmeyer, F4 was found to obey Higuchi, F5 was found to obey Zero order release kinetics, F6 was found to obey Korsmeyer's release kinetics, F7 was found to obey Korsmeyer's release kinetics

9) Buoyancy test

The tablet of formulations F1, F2, F3 and F6 buoyant for 5 hours. Formulations F4, F5, and F7 remained buoyant for a period of 8 hours and are as shown in figure 44 and 45.

Figure 44: Floating ability of Gastro Retentive Formulation of Glimepiride after 1hr

Figure 45: Floating ability of Gastro Retentive Formulation of Glimepiride after 8 hrs

SUMMARY AND CONCLUSION

Glimepiride is second generation new sulfonyl urea oral antidiabetic. Glimepiride is poorly soluble in acidic environment. When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients due to impaired gastric motility or gastric emptying. This erratic absorption of Glimepiride becomes clinically significant, since the efficacy of short acting sulfonylurea is dependent upon the absorption rate of the drug. Hence, to overcome the above mentioned drawbacks the present study aims to develop Glimepiride as Floating Drug Delivery System (FDDS) and its evaluation.

IR Spectroscopy was carried out on pure substances and their physical mixtures to search the possible interaction. The IR Spectrum of pure and physical mixture exhibited there is no interaction between the drug and excipients used for study.

Around 7 formulations weighing 150mg were compressed by varying the proportion of rate controlling polymer (Hypromellose - K4MCR / K100MCR), gel forming polymer (Carbopol).

The granules of different formulations were evaluated for angle of repose, bulk density, and compressibility index. The result of angle of repose indicates reasonably good flow property of granules. The compressibility index values, further support flow property of the granules.

Compressed tablets of all the formulations were evaluated such as physical appearance, thickness and diameter, hardness, friability, weight variation, content uniformity, assay and dissolution. The tablets were circular in shape with no visible cracks with smooth appearance. All the formulations showed reasonably good hardness values. Friability of compressed tablets that lose less than 0.5 to 1% of their weight are generally considered acceptable which indicate that all the formulations compliance with that of standard. Weight variation test revealed that the tablets were within the range of pharmacopeial limit. Content uniformity test compliance that of tablets within the range of pharmacopeial limit. Assay was performed using UV spectroscopy.

The *In vitro* dissolution study was performed for various formulations and marketed formulation. Various formulations were subjected to various model dependent kinetics like Zero order, Higuchi, Korsmeyer release kinetics. The release profile exhibiting maximum r^2 value was found to obey that particular kinetics. It was observed F1 was found to obey Korsmeyer's release kinetics, F2 was found to obey Zero order release kinetics, F3 was found to obey Korsmeyer's release kinetics, F4 was found to obey Higuchi's release kinetics, F5 was found to obey Zero order release kinetics, F6 was found to obey Korsmeyer's release kinetics, F7 was found to obey Korsmeyer's release kinetics.

All the formulations were buoyant, in this formulation F1, F2, F3 and F6 buoyant for 5 hours. Remaining formulations F4, F5 and F7 were found to buoyant for a period of 8 hours.

ABBREVIATIONS

AUC - Area under curve

BMI - Body Mass Index

CDDS - Controlled Drug Delivery System

CL - Clearance

C_{max} - Maximum concentration of drug in plasma

CR - Controlled Release

DMF - Dimethyl Formamide

ER - Extended Release

F - Bioavailability

FDDS - Floating Drug Delivery System

GRDDS - Gastro Retentive Drug Delivery System

HBS - Hydrodynamically Balanced System

IR - Infrared

LBD - Loose Bulk Density

NDDS - Novel Drug Delivery System

SR - Sustained Release

SLS - Sodium Lauryl Sulphate

TBD - Tapped Bulk Density

$T_{½}$ - Biological Half life

UV - Ultraviolet Spectroscopy

Vd - Volume of Distribution

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